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 NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2          "Ask CAS" for self-help around the clock
 NEWS  3  SEP 09  CA/CAplus records now contain indexing from 1907 to the
                  present
 NEWS  4  Jul 15  Data from 1960-1976 added to RDISCLOSURE
 NEWS  5  Jul 21  Identification of STN records implemented
 NEWS  6  Jul 21  Polymer class term count added to REGISTRY
 NEWS  7  Jul 22  INPADOC: Basic index (/BI) enhanced; Simultaneous Left and
                  Right Truncation available
 NEWS  8  AUG 05  New pricing for EUROPATFULL and PCTFULL effective
                  August 1, 2003
 NEWS  9  AUG 13  Field Availability (/FA) field enhanced in BEILSTEIN
 NEWS 10  AUG 15  PATDPAFULL: one FREE connect hour, per account, in
                  September 2003
 NEWS 11  AUG 15  PCTGEN: one FREE connect hour, per account, in
                  September 2003
 NEWS 12  AUG 15  RDISCLOSURE: one FREE connect hour, per account, in
                  September 2003
 NEWS 13  AUG 15  TEMA: one FREE connect hour, per account, in
                  September 2003
 NEWS 14  AUG 18  Data available for download as a PDF in RDISCLOSURE
 NEWS 15  AUG 18  Simultaneous left and right truncation added to PASCAL
 NEWS 16  AUG 18  FROSTI and KOSMET enhanced with Simultaneous Left and Righ
                  Truncation
 NEWS 17  AUG 18  Simultaneous left and right truncation added to ANABSTR
 NEWS 18  SEP 22  DIPPR file reloaded

 NEWS EXPRESS  April 4 CURRENT WINDOWS VERSION IS V6.01a, CURRENT
               MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),
               AND CURRENT DISCOVER FILE IS DATED 01 APRIL 2003
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FILE 'HOME' ENTERED AT 14:14:51 ON 23 SEP 2003

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FILE 'USPATFULL' ENTERED AT 14:15:06 ON 23 SEP 2003
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FILE COVERS 1971 TO PATENT PUBLICATION DATE: 23 Sep 2003 (20030923/PD)
FILE LAST UPDATED: 23 Sep 2003 (20030923/ED)
HIGHEST GRANTED PATENT NUMBER: US6625813
HIGHEST APPLICATION PUBLICATION NUMBER: US2003177560
CA INDEXING IS CURRENT THROUGH 23 Sep 2003 (20030923/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 23 Sep 2003 (20030923/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Aug 2003
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Aug 2003

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>>>  original, i.e., the earliest published granted patents or         <<<
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>>>  publications, starting in 2001, for the inventions covered in     <<<
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>>>  published document but also a list of any subsequent              <<<
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>>>  classifications, or claims, that may potentially change from      <<<
>>>  the earliest to the latest publication.                           <<<

This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> s etodolac and tablet
          1013 ETODOLAC
         63022 TABLET
L1         588 ETODOLAC AND TABLET

=> s l1 and oral (1P) disolv?
        115457 ORAL
          1649 DISOLV?
            23 ORAL (1P) DISOLV?
L2           0 L1 AND ORAL (1P) DISOLV?

=> s l1 and oral  and rapid
        115457 ORAL
        430356 RAPID
L3         314 L1 AND ORAL  AND RAPID

=> s l3 and cellulose?
        202291 CELLULOSE?
L4         274 L3 AND CELLULOSE?

=> s l4 and meloxicam
           406 MELOXICAM
L5         141 L4 AND MELOXICAM
```

```
=> s l5 and rofecoxib
           427 ROFECOXIB
L6          11 L5 AND ROFECOXIB

=> d l6 1-11

L6   ANSWER 1 OF 11  USPATFULL on STN
AN     2003:188396  USPATFULL
TI     P-amidobenzylethers in drug delivery agents
IN     Senter, Peter D., Seattle, WA, UNITED STATES
       Toki, Brian E., Everett, WA, UNITED STATES
PI     US 2003130189      A1   20030710
AI     US 2002-252947     A1   20020923 (10)
RLI    Continuation-in-part of Ser. No. US 2001-963103, filed on 24 Sep 2001,
       PENDING
DT     Utility
FS     APPLICATION
LN.CNT 3203
INCL   INCLM: 514/012.000
       INCLS: 514/008.000; 530/410.000; 530/395.000
NCL    NCLM:  514/012.000
       NCLS:  514/008.000; 530/410.000; 530/395.000
IC     [7]
       ICM: A61K038-16
       ICS: C07K014-00
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6   ANSWER 2 OF 11  USPATFULL on STN
AN     2003:176426  USPATFULL
TI     Methods of treating headaches using 5-HT agonists in combination with
       long-acting NSAIDs
IN     Plachetka, John R., Chapel Hill, NC, United States
PA     Pozen Inc., Chapel Hill, NC, United States (U.S. corporation)
PI     US 6586458         B1   20030701
AI     US 2000-559753          20000427 (9)
RLI    Continuation-in-part of Ser. No. US 1998-151912, filed on 11 Sep 1998,
       now patented, Pat. No. US 6060499 Division of Ser. No. US 1997-907826,
       filed on 14 Aug 1997, now patented, Pat. No. US 5872145
       Continuation-in-part of Ser. No. US 1999-253278, filed on 19 Feb 1999,
       now abandoned
PRAI   US 1996-24129P      19960816 (60)
DT     Utility
FS     GRANTED
LN.CNT 974
INCL   INCLM: 514/415.000
       INCLS: 514/449.000; 514/461.000; 514/473.000
NCL    NCLM:  514/415.000
       NCLS:  514/449.000; 514/461.000; 514/473.000
IC     [7]
       ICM: A61K031-405
EXF    514/449; 514/461; 514/473; 514/415
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6   ANSWER 3 OF 11  USPATFULL on STN
AN     2003:166536  USPATFULL
TI     Vaginally administered anti-dysrhythmic agents for treating pelvic pain
IN     Levine, Howard L., Oceanside, NY, UNITED STATES
       Bologna, William J., Paris, FRANCE
       De Ziegler, Dominique, Geneva, SWITZERLAND
PI     US 2003114394      A1   20030619
AI     US 2002-278912     A1   20021024 (10)
```

PRAI US 2001-330684P 20011029 (60)
DT Utility
FS APPLICATION
LN.CNT 623
INCL INCLM: 514/026.000
INCLS: 514/304.000; 514/211.070; 514/045.000; 514/046.000; 514/305.000; 514/406.000; 514/534.000; 514/355.000; 514/165.000; 514/731.000
NCL NCLM: 514/026.000
NCLS: 514/304.000; 514/211.070; 514/045.000; 514/046.000; 514/305.000; 514/406.000; 514/534.000; 514/355.000; 514/165.000; 514/731.000
IC [7]
ICM: A61K031-7076
ICS: A61K031-704; A61K031-554; A61K031-55; A61K031-46; A61K031-44; A61K031-4745
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 4 OF 11 USPATFULL on STN
AN 2003:57971 USPATFULL
TI Treatment of migraine headache
IN Plachetka, John R., Chapel Hill, NC, UNITED STATES
Chowhan, Zakauddin T., Gaithersburg, MD, UNITED STATES
PA POZEN Inc. (U.S. corporation)
PI US 2003040537 A1 20030227
AI US 2002-255036 A1 20020926 (10)
RLI Division of Ser. No. US 2000-517751, filed on 3 Mar 2000, GRANTED, Pat. No. US 6479551 Continuation-in-part of Ser. No. US 1997-966506, filed on 10 Nov 1997, GRANTED, Pat. No. US 6077539 Continuation-in-part of Ser. No. US 1996-748332, filed on 12 Nov 1996, ABANDONED
PRAI WO 1997-US20611 19971112
DT Utility
FS APPLICATION
LN.CNT 1222
INCL INCLM: 514/406.000
INCLS: 514/619.000
NCL NCLM: 514/406.000
NCLS: 514/619.000
IC [7]
ICM: A61K031-415
ICS: A61K031-165
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 5 OF 11 USPATFULL on STN
AN 2002:329509 USPATFULL
TI **Rapid**-melt compositions methods of making same and methods of using same
IN Cherukuri, S. Rao, Frederick, MD, UNITED STATES
PI US 2002187188 A1 20021212
AI US 2002-208877 A1 20020801 (10)
RLI Continuation-in-part of Ser. No. US 2001-858885, filed on 17 May 2001, PENDING Continuation-in-part of Ser. No. US 2000-610489, filed on 5 Jul 2000, GRANTED, Pat. No. US 6375982
DT Utility
FS APPLICATION
LN.CNT 1233
INCL INCLM: 424/465.000
INCLS: 264/109.000
NCL NCLM: 424/465.000
NCLS: 264/109.000
IC [7]
ICM: A61K009-20
ICS: B27N003-00
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 6 OF 11 USPATFULL on STN
AN 2002:297630 USPATFULL
TI Treatment of migraine headache
IN Plachetka, John R., Chapel Hill, NC, United States
Chowhan, Zakauddin T., Gaithersburg, MD, United States
PA Pozen Inc., Chapel Hill, NC, United States (U.S. corporation)
PI US 6479551 B1 20021112
AI US 2000-517751 20000303 (9)
RLI Continuation-in-part of Ser. No. US 1997-966506, filed on 10 Nov 1997, now patented, Pat. No. US 6077539 Continuation-in-part of Ser. No. US 1996-748332, filed on 12 Nov 1996, now abandoned
PRAI WO 1997-US20611 19971112
DT Utility
FS GRANTED
LN.CNT 1326
INCL INCLM: 514/619.000
INCLS: 424/451.000; 424/457.000; 424/458.000; 424/464.000; 424/468.000; 424/472.000; 514/406.000; 514/569.000; 514/570.000; 514/576.000; 514/577.000; 514/608.000; 514/617.000; 514/646.000; 514/709.000; 514/716.000; 514/717.000; 514/721.000; 514/964.000
NCL NCLM: 514/619.000
NCLS: 424/451.000; 424/457.000; 424/458.000; 424/464.000; 424/468.000; 424/472.000; 514/406.000; 514/569.000; 514/570.000; 514/576.000; 514/577.000; 514/608.000; 514/617.000; 514/646.000; 514/709.000; 514/716.000; 514/717.000; 514/721.000; 514/964.000
IC [7]
ICM: A61K031-16
ICS: A61K009-00; A61K031-00
EXF 514/406; 514/569; 514/570; 514/576; 514/577; 514/608; 514/617; 514/619; 514/646; 514/709; 514/716; 514/717; 514/721; 514/964; 424/468; 424/470; 424/472; 424/473; 424/474; 424/475; 424/480; 424/482; 424/451; 424/457; 424/458
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 7 OF 11 USPATFULL on STN
AN 2002:242824 USPATFULL
TI Combined diffusion / osmotic pumping drug delivery system
IN Faour, Joaquina, Buenos Aires, ARGENTINA
PI US 2002132005 A1 20020919
AI US 2002-47915 A1 20020115 (10)
RLI Continuation-in-part of Ser. No. US 2000-483282, filed on 14 Jan 2000, GRANTED, Pat. No. US 6352721
PRAI WO 2001-US562 20010108
DT Utility
FS APPLICATION
LN.CNT 1705
INCL INCLM: 424/473.000
NCL NCLM: 424/473.000
IC [7]
ICM: A61K009-24
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 8 OF 11 USPATFULL on STN
AN 2002:236069 USPATFULL
TI Method of using COX-2 inhibitors in the treatment and prevention of ocular COX-2 mediated disorders
IN Bandyopadhyay, Rebanta, Portage, MI, UNITED STATES
Eveleth, David, East Brunswick, NJ, UNITED STATES
Van Haarlem, Thomas Joseph, Clinton, NJ, UNITED STATES
Kararli, Tugrul T., Skokie, IL, UNITED STATES
Singh, Satish K., Portage, MI, UNITED STATES

PI US 2002128267 A1 20020912
AI US 2001-849683 A1 20010504 (9)
PRAI US 2000-218101P 20000713 (60)
US 2001-279285P 20010328 (60)
DT Utility
FS APPLICATION
LN.CNT 2387
INCL INCLM: 514/247.000
INCLS: 514/406.000; 514/456.000; 514/471.000; 514/684.000
NCL NCLM: 514/247.000
NCLS: 514/406.000; 514/456.000; 514/471.000; 514/684.000
IC [7]
ICM: A61K031-415
ICS: A61K031-50; A61K031-12; A61K031-353
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 9 OF 11 USPATFULL on STN
AN 2002:55008 USPATFULL
TI Clear oil-containing pharmaceutical compositions containing a therapeutic agent
IN Chen, Feng-Jing, Salt Lake City, UT, UNITED STATES
Patel, Mahesh V., Salt Lake City, UT, UNITED STATES
Fikstad, David T., Salt Lake City, UT, UNITED STATES
PI US 2002032171 A1 20020314
AI US 2001-877541 A1 20010608 (9)
RLI Continuation-in-part of Ser. No. US 1999-345615, filed on 30 Jun 1999, GRANTED, Pat. No. US 6267985 Continuation-in-part of Ser. No. US 2000-751968, filed on 29 Dec 2000, PENDING Continuation-in-part of Ser. No. US 1999-375636, filed on 17 Aug 1999, GRANTED, Pat. No. US 6309663
DT Utility
FS APPLICATION
LN.CNT 4418
INCL INCLM: 514/054.000
INCLS: 424/727.000; 424/731.000; 424/750.000; 424/757.000
NCL NCLM: 514/054.000
NCLS: 424/727.000; 424/731.000; 424/750.000; 424/757.000
IC [7]
ICM: A61K031-715
ICS: A61K035-78
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 10 OF 11 USPATFULL on STN
AN 2002:12064 USPATFULL
TI **Rapid**-melt semi-solid compositions, methods of making same and methods of using same
IN Cherukuri, Subraman Rao, Vienna, VA, UNITED STATES
PI US 2002006440 A1 20020117
US 6589556 B2 20030708
AI US 2001-858885 A1 20010517 (9)
RLI Continuation-in-part of Ser. No. US 2000-610489, filed on 5 Jul 2000, PENDING
DT Utility
FS APPLICATION
LN.CNT 1583
INCL INCLM: 424/465.000
NCL NCLM: 424/484.000
NCLS: 424/488.000
IC [7]
ICM: A61K009-20
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 11 OF 11 USPATFULL on STN

AN 2000:50705 USPATFULL
TI Method for treating or preventing chronic nonbacterial prostatitis and prostatodynia
IN Guess, Harry A., Chapel Hill, NC, United States
Waldstreicher, Joanne, Scotch Plains, NJ, United States
Pearson, Jay Dee, Hatfield, PA, United States
PA Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)
PI US 6054455 20000425
AI US 1999-313002 19990517 (9)
PRAI US 1998-85866P 19980515 (60)
DT Utility
FS Granted
LN.CNT 2051
INCL INCLM: 514/231.200
INCLS: 514/326.000
NCL NCLM: 514/231.200
NCLS: 514/326.000
IC [7]
ICM: A61K031-535
ICS: A61K031-445
EXF 514/326; 514/231.2
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d l6 1-11 kwic

L6 ANSWER 1 OF 11 USPATFULL on STN
SUMM . . . a hydroxyl group of a drug is linked to a spacer via a labile carbonate linkage that is susceptible to **rapid** hydrolysis in aqueous buffer or human serum, the drug conjugates of the present invention utilizing a benzyl ether linkage are. . .
DETD . . . composition may be in the form of a solid, liquid or gas (aerosol). Typical routes of administration include, without limitation, **oral**, topical, parenteral, sublingual, rectal, vaginal, ocular, and intranasal. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal. . . that will be administered to a subject take the form of one or more dosage units, where for example, a **tablet** may be a single dosage unit, and a container of a compound of the invention in aerosol form may hold. . .
DETD . . . in admixture with one or more carriers. The carrier(s) may be particulate, so that the compositions are, for example, in **tablet** or powder form. The carrier(s) may be liquid, with the compositions being, for example, an **oral** syrup or injectable liquid. In addition, the carrier(s) may be gaseous, so as to provide an aerosol composition useful in,. . .
DETD [0195] When intended for **oral** administration, the composition is preferably in either solid or liquid form, where semi-solid, semi-liquid, suspension and gel forms are included. . .
DETD [0196] As a solid composition for **oral** administration, the composition may be formulated into a powder, granule, compressed **tablet**, pill, capsule, chewing gum, wafer or the like form. Such a solid composition will typically contain one or more inert. . . or edible carriers. In addition, one or more of the following adjuvants may be present: binders such as carboxymethylcellulose, ethyl **cellulose**, microcrystalline **cellulose**, or gelatin; excipients such as starch, lactose or dextrins, disintegrating agents such as alginic acid, sodium alginate, Primogel, corn starch. . .
DETD . . . be in the form of a liquid, e.g., an elixir, syrup, solution, emulsion, or suspension. The liquid may be for **oral** administration or for delivery by injection, as two examples. When intended for **oral** administration, preferred composition contain, in addition to the present compounds, one or more of a

sweetening agent, preservatives, dye/colorant and. . .

DETD [0200] A liquid composition intended for either parenteral or **oral** administration should contain an amount of a compound of the present invention such that a suitable dosage will be obtained.. . . precise dose will depend in large part on the drug selected for incorporation into the inventive conjugates. When intended for **oral** administration, this amount may be varied to be between 0.1% and about 80% of the weight of the composition. Preferred **oral** compositions contain between about 4% and about 50% of the compound of the invention. Preferred compositions and preparations according to. . .

DETD . . . colon cancer
colorectal cancer
kidney cancer
pancreatic cancer
bone cancer
breast cancer
ovarian cancer
prostate cancer
esophogeal cancer
stomach cancer
oral cancer
nasal cancer
throat cancer
squamous cell carcinoma
basal cell carcinoma
adenocarcinoma
sweat gland carcinoma
sebaceous gland carcinoma
papillary carcinoma

. . .

DETD . . . A
mycophenylate mofetil
sirolimus
tacrolimus
enanercept
prednisone
azathioprine
methotrexatecyclophosphamide
prednisone
aminocaproic acid
chloroquine
hydroxychloroquine
hydrocortisone
dexamethasone
chlorambucil
DHEA
danazol
bromocriptine
meloxicam
infliximab

DETD . . . dextromethorphan, phenazocine, pentazocine, cyclazocine, methadone, isomethadone and propoxyphene. Suitable non-opioid analgesic agents include, but are not limited to, aspirin, celecoxib, **rofecoxib**, diclofinac, diflusinal, **etodolac**, fenoprofen, flurbiprofen, ibuprofen, ketoprofen, indomethacin, ketorolac, meclofenamate, mefanamic acid, nabumetone, naproxen, piroxicam and sulindac.

L6 ANSWER 2 OF 11 USPATFULL on STN

SUMM Among the preferred long-acting NSAIDs for use in compositions and methods are: naproxen, flurbiprofen, ketoprofen, oxaprozin,

etodolac, indomethacin, ketorolac, nabumetone, mefanamic acid, and piroxican. Of these, the most preferred is naproxen or a pharmaceutically acceptable salt of. . .

SUMM . . . use with any of the above compositions and methods are the cyclooxygenase-2 (COX-2) inhibitors. Members of this group include: celecoxib; **rofecoxib**; **meloxicam**; JTE-522; L-745,337; NS398; and pharmaceutically acceptable salts thereof. The most preferred is celecoxib in an amount of between 50 and. . .

SUMM . . . to 15 hours and about 12 to 13 hours respectively; oxaprozin with a half-life of about 42 to 50 hours; **etodolac** with a half-life of about 7 hours; indomethacin with a half-life of about 4 to 6 hours; ketorolac with a. . .

SUMM . . . those skilled in the art. It is to be further understood that drug dosages are, in particular instances, measured as **oral**, or parenteral or inhaled dosages or with reference to drug levels as measured in blood.

SUMM Sumatriptan is usefully provided as **oral** tablets of 25 mg, 50 mg and 100 mg and as a parenteral dosage form containing about 6 mg/ml and about 6 mg/0.5 ml for subcutaneous administration. **Oral** doses of about 1-300 mg are also useful with particular reference to doses of about 10-100 mg. Peak serum concentrations. . .

SUMM Ergotamine tartrate in **oral** doses of about 1 to 5 mg with particular reference to about 1-2 mg are useful, as are doses of about 1-2 mg at 30 minute intervals, up to about 6 to 8 mg in one day. **Oral** inhalation of sequential doses of about 0.1 to 0.5 mg at intervals of about 5 minutes are noted, with particular. . .

SUMM Ergonovine maleate may be administered by injection of about 0.2 mg/ml, and **oral** tablets of about the same strength may also be given.

SUMM . . . useful when contained in tablets of from about 25 to 75 mg, in suppositories of about 50 mg, and in **oral** suspensions of about 25 mg/5 ml. A typical daily **oral** dosage of indomethacin is three 25 mg doses taken at intervals during one day, amounting to 75 mg total. However,. . .

SUMM Naproxen is particularly useful when contained in tablets of from about 250 to about 500 mg and in **oral** suspensions of about 125 mg/5 ml. For naproxen sodium, tablets of about 275 or about 550 mg are particularly useful.. . .

SUMM **Etodolac** is usefully provided in capsules of 200 mg and 300 mg or in tablets of 400 mg. Useful doses for. . .

SUMM . . . tablets of 10 mg and as a sterile parenteral preparation for injection in 15 mg/ml and 30 mg/ml dosage forms. **Oral** doses of up to 40 mg with particular reference to 10-30 mg per day and parenteral doses up to 120-150. . .

SUMM . . . mg per day (see, Bolten, J., Rheumatolog. Suppl., 51:2-7 (May, 1998)). Celecoxib peak plasma concentrations occur approximately 3 hours after **oral** dosing. The effective half-life is approximately 11 hours. In one embodiment, coordination and co-timely administration of a 5-HT agonist is. . .

SUMM **Rofecoxib** (Vioxx.RTM.) for **oral** administration is available in tablets of 12.5, 25 or 50 mg and in an **oral** suspension containing either 12.5 mg or 25 mg **rofecoxib** per 5 ml. The recommended initial daily dosage for the management of acute pain is 50 mg. Peak plasma concentrations of **rofecoxib** typically occur about 2-3 hours after **oral** administration and the drug has a half life of about 17 hours.

SUMM . . . of COX-2 and the resultant decreases in pro-inflammatory prostaglandins, like thromboxane. Drugs which selectively inhibit the COX-2 isozyme, like celecoxib, **rofecoxib**, **meloxicam**, piroxicam, JTE-522 and L-745,337, produce analgesia and reduce inflammation without removing the protective prostaglandins in the stomach and kidney.

SUMM 4. Furst, Semin. Arthritis. Rheum 26 (6 Suppl 1):21-7 (1997). Note

particularly the dosage range of **meloxicam** at about 7.5 mg per day or more, and including 15 mg per day in arthritis pain indications.

SUMM . . . multiple routes of administration may be employed, e.g., intravenous or subcutaneous injection of a 5-HT agonist may be combined with **oral** administration of a long acting NSAID.

SUMM . . . at about 2 to 4 hours and 1 to 2 hours respectively; oxaprozin peaks at about 3 to 5 hours; **etodolac** peaks at about 1 to 2 hours; indomethacin peaks at about 1 to 4 hours; ketorolac peaks about one-half to. . .

SUMM H. "Unit dosage from" shall mean a single drug administration entity. By way of example, a single **tablet**, capsule, dragee, or trochee, suppository, or syringe combining both a 5-HT agonist and an NSAID would be a unit dosage. . .

SUMM . . . blood levels over the time periods specified above. It is preferred that the dosage form provide blood levels consistent with **rapid** initial headache or migraine relief and a reduced incidence of relapse headache.

SUMM I. "Quick dissolve" in reference to a **tablet** or other **oral** dosage form shall mean that the **oral** dosage form is at least 95% dissolved within 20 minutes after administration. In determining "quick dissolve," reference is made to. . .

SUMM . . . guideline. Maximum daily dosages in milligrams are as follows: flurbiprofen 300; ketoprofen 300; naproxen 1500, naproxen sodium 1375; oxaprozin 1800; **etodolac** 1200; indomethacin 150 to 200; ketorolac 120 mg i.m. and 40 **oral**; nabumetone 2000; mefenamic acid 1000; and piroxicam 20. In particular instances, however, exceeding these "maximum" doses is the therapeutic choice. . .

DETD . . . migraine attack consisting of typical migraine headache, nausea and sensitivity to light and sound. She is dosed with a single **oral tablet** containing sumatriptan 25 mg and naproxen sodium 550 mg. Her symptoms start to diminish within one hour and by three. . .

DETD . . . She is dosed with a single subcutaneous injection of sumatriptan 6 mg and at the same time orally ingests a **tablet** containing naproxen sodium 550 mg. Her symptoms start to diminish within 20 minutes and by two hours she is completely. . .

DETD . . . migraine attack consisting of typical migraine headache, nausea and sensitivity to light and sound. She is dosed with a single **oral tablet** containing 12.5 mg sumatriptan and 550 mg naproxen sodium. Her symptoms start to diminish within one hour. By three hours. . .

DETD . . . to light and sound. She is dosed with a single subcutaneous injection of 2 mg sumatriptan and orally ingests a **tablet** containing 550 mg naproxen sodium. Her symptoms start to diminish within 30 minutes and by two hours she is completely. . .

DETD . . . of age offers the same presenting history and indication as in Example 1. Treatment is by means of a single **oral tablet** containing 50 mg sumatriptan and 550 mg naproxen. The same result as in Example 1 is obtained.

DETD A variety of combinations of 5-HT agonists and NSAIDs can be made into a single dosage form, either **tablet**, capsule, suppository, parenteral or other. As an example, a rapidly dissolving **tablet** of 0.5 mg ergotamine tartrate combined with 550 mg naproxen sodium is conveniently available for use. Another example includes a rapidly dissolving **tablet** of 12.5 mg of sumatriptan combined with 550 mg of naproxen sodium. Other agents may also be present such as: pregelatinized maze starch, polyvinyl-pyrrolidone or hydroxypropyl methylcellulose; fillers (e.g., lactose, microcrystalline **cellulose** or calcium phosphate); disintegrants (e.g., potato starch, croscarmellose sodium, or sodium starch glycollate); wetting agents (e.g., sodium lauryl sulphate) or. . .

DETD . . . be made up of various agents listed herein. As an example, in

the case of naproxen sodium and sumatriptan, several **tablet** strengths are available including: 12.5 mg sumatriptan/550 mg naproxen sodium; 25 mg sumatriptan/550 mg naproxen sodium; 12.5 mg sumatriptan/275 mg naproxen sodium; and 25 mg sumatriptan/275 naproxen sodium. Each **tablet** dissolves within 20 minutes to rapidly produce effective blood levels of each component.

DETD . . . are employed in admixture with conventional excipients, i.e., pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral, enteral (e.g., **oral** or intranasal) or topical application which do not deleteriously react with the active compositions. Suitable pharmaceutically acceptable carriers include but. . .

CLM What is claimed:

. . . composition of any one of claims 1-5, wherein said 5-HT agonist is sumatriptan, and said LA-NSAID is naproxen in an **oral** unit dosage form comprising sumatriptan in an amount of greater than 25 mg and naproxen in an amount of greater. . .

. . . of any one of claims 1-5, wherein said LA-NSAID is selected from the group consisting of flurbiprofen, ketoprofen, naproxen, oxaprozin, **etodolac**, indomethacin, ketorolac, nabumetone, mefanamic acid, and piroxicam.

27. The pharmaceutical composition of claim 26, wherein: a) said pharmaceutical composition is suitable for **oral** administration; b) said sumatriptan is present in an amount of between 25 and 100 mg; and c) said naproxen is. . .

30. The pharmaceutical composition of claim 29, wherein: a) said pharmaceutical composition is suitable for **oral** administration; b) said sumatriptan is present in an amount of between 25 and 100 mg; and c) said naproxen is. . .

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SUMM . . . associated with uterine dysrhythmic conditions, including dysmenorrhea. See, e.g., U.S. patent application Ser. No. 10/089,796. Uterine dysrhythmias may affect the **rapid** transport of sperm, thus affecting fertility. Contractility along the female tract (uterus and fallopian tubes) appears to be the primary motor assuring **rapid** transport of sperm from the cervical area to the distal end of the tubes, where fertilization takes place. Retrograde uterine. . .

SUMM [0024] NSAIDS include, for example, diclofenac, **etodolac**, fenoprofen, lurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, fenamic acid, **meloxicam**, nabumetone, naproxin, oxaprozin, piroxicam, sulindac, and tolmetin.

SUMM [0025] COX inhibitors include, for example, aspirin, celecoxib, **rofecoxib**, and valdecoxib.

SUMM . . . be formulated as any appropriate vaginal composition, such as, without limitation, a gel or cream, or even as a gelifying **tablet** for administration. When administered, the composition diffuses through the vaginal mucosal into the target tissue. Relief from pain is provided. . .

SUMM [0042] The bioadhesive formulation may be in the form of a gel, cream, **tablet**, pill, capsule, suppository, film, or any other pharmaceutically acceptable form that adheres to the mucosa and does not wash away. . .

SUMM . . . of the patient. Such additives include, without limitation, one or more of the following: lubricants, plasticizing agents, preservatives, gel formers, **tablet** formers, pill formers, suppository formers, film formers, cream formers, disintegrating agents, coatings, binders, vehicles, coloring agents, odor controlling agents, humectants,. . .

SUMM . . . In a preferred embodiment, the anesthetic is used in its basic

form and is suspended in a gel or gelafying **tablet** for delivery.

SUMM [0048] Typical **oral** or injection forms of anesthetics would need to achieve high blood levels in order to reach uterine tissue levels sufficient. . .

DETD . . . Carbopol 974P, but may be substituted by other gel formers including, but not limited to Carbopol 934P, Carbopol 980, methyl **cellulose** or propyl **cellulose**.

DETD [0053] NATROSOL.RTM. 250 HHX is a viscosity-enhancing agent, but may be substituted by other viscosity-enhancing agents, such as methyl **cellulose** or propyl **cellulose**.

CLM What is claimed is:

. . . digoxin, digitoxin, adenosine, propranolol, esmolol, N-acetyl procainamide, amlodipine, bepridil, diltiazem, felodipine, isradipine, nicardipine, nifedipine, nimodipine, verapamil, pirmagrel, dazoxiben, zileuton, diclofenac, **etodolac**, fenoprofen, lurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, fenamic acid, **meloxicam**, nabumetone, naproxin, oxaprozin, piroxicam, sulindac, tolmetin, aspirin, celecoxib, **rofecoxib**, and valdecoxib.

. . . digoxin, digitoxin, adenosine, propranolol, esmolol, N-acetyl procainamide, amlodipine, bepridil, diltiazem, felodipine, isradipine, nicardipine, nifedipine, nimodipine, verapamil, pirmagrel, dazoxiben, zileuton, diclofenac, **etodolac**, fenoprofen, lurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, fenamic acid, **meloxicam**, nabumetone, naproxin, oxaprozin, piroxicam, sulindac, tolmetin, aspirin, celecoxib, **rofecoxib**, and valdecoxib.

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SUMM . . . typically: aspirin, 500-650 mg; acetaminophen, 500 mg; naproxen sodium, 750-825 mg; tolfenamic acid, 200-400 mg; and, ibuprofen 200 mg. After **oral** dosing, peak plasma concentrations in normal subjects usually occur at about 1 hour for aspirin and acetaminophen, and between 1. . .

SUMM [0006] Metoclopramide is a drug known to relieve migraine-associated nausea when administered at a minimum **oral** dose of 10 mg. Poyser et al. have described a formulation in which aspirin is uniformly intermixed with metoclopramide (U.S.. . .

SUMM [0008] In its first aspect, the present invention is directed to a pharmaceutical composition in unit dosage form suitable for **oral** administration in the treatment of migraine headache. The dosage form contains metoclopramide in an amount effective to increase gastric motility. . . non-acidic NSAID) in an amount effective to reduce or eliminate headache pain. Preferably, the dosage form should be either a **tablet** or capsule and should be free from vasoactive agents, including 5 HT agonist vasoactive agents. The dosage form may be. . .

SUMM . . . which either metoclopramide or analgesic is barrier coated. Alternatively, metoclopramide and analgesic may be in separate layers of a multilayer **tablet**. Dosage forms should typically be free of vasoactive agents, may be coordinated and may contain either long-acting NSAIDs or NSAIDs formulated to be long acting. Typical NSAIDs that may be used include: acetaminophen; ibuprofen; flurbiprofen; ketoprofen; naproxen; oxaprozin; **etodolac**; indomethacin; ketorolac; nabumetane; piroxicam; celecoxib; **rofecoxib**; **meloxicam** ; JTE-522; L-745,337; NS398; and pharmaceutically acceptable salts thereof. The most preferred analgesic is naproxen. This should be present at between. . .

SUMM . . . reduce or eliminate headache pain. Long acting NSAIDs suitable for use in the dosage forms include: ibuprofen; flurbiprofen;

ketoprofen; oxaprozin; **etodolac**; indomethacin; ketorolac; nabumetane; piroxicam; celecoxib; **rofecoxib**; **meloxicam** ; JTE-522; L-745,337; NS398; or pharmaceutically acceptable salts thereof. When naproxen, the preferred analgesic, is used, it should be present in. . . of Controlled Drug Delivery, Edith Mathiowitz, John Wiley & Sons (1999), ISBN: 0471148288). Coordinated dosage forms should be suitable for **oral** delivery and will typically take the form of a **tablet** or capsule. Metoclopramide and NSAID may be in separate layers of a multilayer **tablet** and, in general, these dosage forms should be substantially free of vasoactive agents such a 5 HT agonists.

SUMM . . . or NSAIDs formulated to be long acting) may be acid-base storage stabilized or coordinated and should, preferably, be suitable for **oral** administration (e.g. in the form of a **tablet** of capsule). It will also generally be advantageous for metoclopramide to be present at a concentration effective to reduce or. . .

SUMM . . . the method. NSAIDS that can be used include: acetaminophen (when formulated to be long acting); ibuprofen; flurbiprofen; ketoprofen; naproxen; oxaprozin; **etodolac**; indomethacin; ketorolac; nabumetane; piroxicam; celecoxib; **rofecoxib**; **meloxicam**; JTE-522; L-745,337; NS398; orpharmaceutically acceptable salts thereof. In general, naproxen is the most preferred NSAID, particularly when in the form. . .

DRWD [0017] FIG. 4. is a comparative dissolution plot of the metoclopramide presented in a **tablet** coating layer and presented in a compressed **tablet** layer.

DRWD [0018] FIG. 5a is a plot of plasma concentrations of metoclopramide upon administration of **tablet**(s) of the present invention as disclosed in **Tablet** Example 4.

DRWD [0019] FIG. 5b is a plot of plasma concentrations of naproxen sodium upon administration of **tablet**(s) of the present invention as disclosed in **Tablet** Example 4.

DRWD [0020] FIG. 6 is a diagrammatic cross section side view of a **tablet** coating pan with baffles and spray nozzles.

DETD . . . that serves as a barrier to prevent interaction or the drugs may be segregated into different layers of a multilayer **tablet** . Methods for producing "acid-base storage stabilized" dosage forms are described in the Examples section below. Such dosage forms may, of. . .

DETD . . . is preferred that formulations for the treatment of patients be free from vasoactive agents and that they be suitable for **oral** administration.

DETD [0030] The Making of **Tablet** Dosage Forms

DETD [0031] The combination of metoclopramide and an analgesic may take place in a single layer **tablet** or other solid dosage form. A bi- or multi layer **tablet** of the type described in this invention relieves nausea, improves gastrointestinal motility which enhances the speed of absorption of the. . .

DETD [0032] In a bilayer configuration, one portion of the **tablet** contains metoclopramide in the required dose and appropriate excipients, agents to aid dissolution, lubricants, fillers, etc., and is, preferably, designed. . . in the stomach in less than about 10 minutes, thus increasing gastrointestinal motility and controlling nausea. The effect of the **rapid** availability of metoclopramide is to accelerate delivery of the naproxen (or other analgesic) to the small intestine which is the site of most **rapid** absorption. In a bilayer **tablet** embodiment, the second portion of the **tablet** will contain, preferably, naproxen sodium in the required dose and appropriate excipients, agents to aid dissolution, lubricants, fillers, etc. It. . .

DETD [0033] In one embodiment of bilayer **tablet** preparation, once the two components have been manufactured, they are combined into a

single **tablet**. This process allows for different dosages of either component (i.e. the metoclopramide component or the naproxen sodium component) to be usefully combined into a single **tablet** in an efficient way. In another embodiment, substantially each naproxen sodium crystal (or metoclopramide particle) is coated with a **rapid** dissolving excipient material, conveniently, prior to tableting.

DETD [0034] Powder flow characteristics and powder compressibility are the main criteria to be considered with respect to successful **tablet** production. To improve compressibility, naproxen sodium may be granulated. This involves increasing granule size through the addition of excipients that. . .

DETD . . . forms should be used, e.g., the acidic analgesic and the metoclopramide may be sequestered to different layers of a multilayer **tablet** in such a manner that contact between the drugs is eliminated or minimized. In the case of COX-2 inhibitors, the. . . when contained in tablets of from about 100 to 200 mg. Celecoxib peak plasma concentrations occur approximately 3 hours after **oral** dosing. The effective half-life is approximately 11 hours.

DETD . . . to 15 hours and about 12 to 13 hours respectively; oxaprozin with a half-life of about 42 to 50 hours; **etodolac** with a half-life of about 7 hours; indomethacin with a half-life of about 4 to 6 hours; ketorolac with a. . .

DETD . . . those skilled in the art. It is to be further understood that drug dosages are, in particular instances, measured as **oral** dosages, or parenteral or inhaled dosages or with reference to drug levels as measured in blood.

DETD . . . at least 10 mg by injection i.m. or intravenously to be useful for the treatment of the nausea accompanying migraine. **Oral** doses of 10-20 mg are less useful because it takes longer for therapeutic blood levels to be reached, resulting in. . .

DETD . . . a range of from about 25 to 75 mg, when present in suppositories at about 50 mg, and when in **oral** suspensions at a concentration of about 25 mg/5 ml. A typical daily **oral** dosage of indomethacin is three 25 mg doses taken at intervals during one day. However, daily doses of up to. . .

DETD [0043] Naproxen is particularly useful when contained in tablets of from 250 to 500 mg, and in **oral** suspensions of about 125 mg/5 ml. For naproxen sodium, tablets of about 275 or about 550 mg are particularly useful.. . .

DETD [0045] **Etodolac** is usefully provided in capsules of 200 mg and 300 mg and in tablets of 400 mg. Useful doses for. . .

DETD . . . tablets of 10 mg and as a sterile parenteral preparation for injection in 15 mg/ml and 30 mg/ml dosage forms. **Oral** doses of up to 40 mg, and particularly 10-30 mg per day and parenteral doses up to 120-150 mg per. . .

DETD [0050] One particular group of long acting NSAIDs that may be used are the cyclooxygenase-2 ("COX-2") inhibitors, for example: celecoxib, **rofecoxib**, **meloxicam**, piroxicam, JTE-522, L-745,337, or NS398, or pharmaceutically acceptable salts thereof. JTE-522, L-745,337 and NS398 are described, inter alia, in Wakitani,. . . al., Jpn. J. Pharmacol. 78:365-371 (1998); and Panara, et al., Br. J. Pharmacol. 116:2429-2434 (1995). The amount present in a **tablet** or administered to a patient will depend upon the particular COX-2 inhibitor being used. For example, piroxicam may be present at 10 to 20 mg per **tablet**. Celecoxib may be administered to a human in an amount of from about 100 mg to about 500 mg or. . .

DETD . . . an effective local gastrointestinal concentration. In a preferred embodiment of co-timely drug administration, both drugs are administered in a single **oral** unit dosage form.

DETD . . . at about 2 to 4 hours and 1 to 2 hours respectively; oxaprozin peaks at about 3 to 5 hours; **etodolac** peaks at about 1 to 2

hours; indomethacin peaks at about 1 to 4 hours; ketorolac peaks at about one-half. . .

DETD [0056] G. "**Rapid** availability" as to metoclopramide in an **oral** dosage form shall be understood to be essentially the complete solubilization of metoclopramide from the dosage form within 30 minutes and preferably within 5 minutes from ingestion. Clearly, an **oral** dosage form of metoclopramide which is liquid at the time of administration would also represent a "**rapid** availability" form.

DETD [0064] N. "Unit dosage form" shall mean single drug administration entity. By way of example, a single **tablet**, capsule, dragee, or trochee (**oral** unit dosage forms), suppository, or syringe combining both metoclopramide and an NSAID would be a unit dosage form. Administration of. . .

DETD . . . professional. Maximum daily doses in milligrams is as follows: flurbiprofen 300; ketoprofen 300; naproxen 1500, naproxen sodium 1375; oxaprozin 1800; **etodolac** 1200; indomethacin 150 to 200; ketorolac 120 mg i.m. and 40 **oral**; nabumetane 2000; mefenamic acid 1000; and piroxicam 20.

DETD . . . levels of metoclopramide. The data was obtained from 10 healthy volunteer subjects. On day 1, the subjects were administered one **tablet** of 500 mg naproxen sodium and 8 mg metoclopramide prepared as described in the Examples section. On day 4, two. . .

DETD Example 1: **Tablet** Formulation #1

DETD [0071] A variety of combinations of metoclopramide and analgesic can be made into a single dosage form (e.g., **tablet**, capsule, suppository) consisting of one or more layers. In this example, a sequentially and rapidly dissolving single layer **tablet** of metoclopramide, 8 mg, is combined with naproxen sodium, 500 mg. Referring to FIG. 1, this single layer **tablet** contains naproxen sodium in crystalline form (2) and metoclopramide (4), each uniformly distributed throughout a matrix (6) of pharmaceutically acceptable fillers, excipients, binding agents, disintegrants, and lubricants (collectively, "carrier material"). A pharmaceutically acceptable **tablet** coating (8) surrounds the active ingredients and carrier materials. Carrier material should be present in an amount of between 50 and 2000 mg, and preferably between 500 and 1,000 mg. Prior to compaction in a **tablet**, each crystal of naproxen sodium may optionally be coated with excipient. Tablets may include microcrystalline **cellulose** and magnesium stearate. For example, naproxen sodium may be coated with hydroxypropyl methylcellulose 2910 and polyethylene 8000. A core bulking. . . Opadry.RTM. YS-1-4215 (trademarks of Colorcon, West Point, Pa.). Povidone and talc may also be used as bulking agents for the **tablet** core.

DETD [0072] **Tablet** stability is compromised in instances in which there is an "acid-base incompatibility" between the metoclopramide and the analgesic. For example,. . . The basic salt of metoclopramide intimately mixed with acidic naproxen sodium crossreacts in a matter of days causing reduction in **tablet** potency of about 5% in two weeks and about 20 to 25% or more in three weeks at ambient temperature.. . . applied in combination with water for irrigation and talc. Other materials are shellac, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, and **cellulose** acetate phthalate. Thin coatings, on the order of about 25-250 microns, retard the availability of naproxen by no more than. . .

DETD Example 2: **Tablet** Formulation #2

DETD [0073] FIG. 2. depicts a sequentially and rapidly dissolving bilayer **tablet** of metoclopramide, 16 mg, combined with naproxen sodium 500 mg. The **tablet** consists of a first layer (11) and a second layer (13). The first layer (11) contains naproxen sodium in crystalline. . . a matrix (17) of pharmaceutically acceptable

fillers, excipients, binding agents, disintegrants, and lubricants (collectively, "second carrier material"). A pharmaceutically acceptable **tablet** coating (18) surrounds the active ingredients and carrier materials. Dotted line 15 represents the interface between the two layers which are separately molded, poured, compressed or otherwise formed and joined by compression or other **tablet** forming means. The first carrier material and the second carrier material may be either the same or different.

DETD Example 3: **Tablet** Formulation #3

DETD [0075] A particular example of a **tablet** in which metoclopramide is in an effervescent matrix separated from analgesic is as follows:

DETD [0077] B. Naproxen: 500 mg of naproxen sodium are compacted as granules with: povidone k-29/32 (23.6 mg); microcrystalline **cellulose**, NF (105.9 mg); croscarmellose sodium, NF, (13.5 mg); talc (27 mg); and magnesium stearate (5 mg).

DETD [0078] C. The metoclopramide granules and the naproxen are combined into a two-layer **tablet** as described in Example 2.

DETD Example 4: **Tablet** Formulation #4

DETD [0079] FIG. 3. depicts another example of a sequentially and rapidly dissolving bilayer **tablet** in which metoclopramide hydrochloride (8 mg) is combined with naproxen sodium (500 mg). Referring to the figure, the bilayer **tablet** consists of a first layer (311) and a second layer (313) having an exterior portion (317) and an interior portion. . . crystalline form 314) uniformly distributed throughout the exterior portion of layer (313), wherein (317) comprises a matrix of pharmaceutically acceptable **tablet** coating. A **tablet** coating (317) surrounds both the second layer as well as the layer of naproxen and carrier material (311). Dotted line. . . interface between the exterior portion (313) and the interior portion (319). This interface may comprise titanium dioxide, camauba wax, shellac, **cellulose** acetate phthalate or the like. Interior portion (319) may comprise about 2 to 3% of the coating material of (313). . .

DETD . . . The naproxen-containing portion of tablets may be separately molded, poured, compressed or otherwise formed and joined by compression or other **tablet** forming means. It is then spray coated with a material absent metoclopramide, e.g., HPMC, triethyl citrate, and TiO2 applied in. . .

DETD [0081] Preparation of a **tablet** of FIG. 3 requires particular attention to the application of metoclopramide in such a manner as to maintain acceptable **tablet** dosage uniformity ("uniform-coated unit dosage form"). Coating should be uniform to between 85% and 115% of the intended dosage with. . . deviation of 6.4 or less. With pancoating methodology, it is important to control pan speed, movement of tablets across the **tablet** bed, spray temperature and spray coverage relative to the entire pan. Tablets sticking to each other or to the pan. . .

DETD [0082] FIG. 6 depicts an apparatus for coating tablets. A rotating coating pan (602) is partially filled with **tablet** cores to be coated. In the embodiment shown, screen panels (604) facilitate air circulation, and baffles (608) placed on the coating pan walls agitate **tablet** cores during rotation. Spray nozzles (612) and (614)) leading from a spray mixture reservoir, and pump means spray coating through an inlet (610) over **tablet** cores. An air source (618) introduces drying air into the coating pan from a heating and pumping source (not shown).. . .

DETD . . . Franklin Park Ill.)). Using two spray guns about 10 to 12 inches apart and 4 to 8 inches above the **tablet** bed should produce a suitable coating when pans are rotated at a speed of 14 to 16 rpm. It is particularly important to maintain **tablet** movement in the pan to avoid **tablet** sticking and enhance coating

uniformity.

DETD Example 5: **Tablet** Formulation #5 (Metoclopramide film coated **tablet**)

DETD [0084] This acid-base storage stable uniform-coated unit dosage form has metoclopramide as a film in the outermost portion of the **tablet** and separated from the naproxen sodium. The final **tablet** formulation by weight is as follows:

A.	metoclopramide hydrochloride		8 mg
	(i)	metoclopramide-containing coating (in percentage of total. . . citrate	0.1% .+-. 0.5%
		metoclopramide	26% .+-. 1%
		talc	24% .+-. 1%
	(ii)	metoclopramide free coating (in percentage of total **tablet** dry weight)	
		hydroxypropyl methylcellulose	9%
		titanium dioxide	1%
		triethyl citrate	2%
B.	naproxen core		
	naproxen sodium		500 mg
	povidone k-29/32		23.6 mg
	microcrystalline **cellulose**, NF,		105.9 mg
	croscarmellose sodium, NF		13.5
	talc		27 mg
	magnesium stearate		5 mg

DETD [0085] To prepare a two layer **tablet** as in FIG. 3., particular attention is paid to the application of the film coating. Naproxen cores are placed in. . . 14-16 rpm. From two spray guns mounted about 4 to 8 inches apart and 10 to 12 inches above the **tablet** bed, atomized metoclopramide-free coating mixture is sprayed over the rotating pan until the cores increase from about 2% to about. . .

DETD . . . step, tablets are again spray coated in the rotating baffled pan, but now with a metoclopramide-containing coating material until the **tablet** weight increases from about 8 to about 10% over the weight of the naproxen core. For example, sufficient spraying may be performed to apply 8 mg of metoclopramide to each **tablet**.

DETD . . . "uniform-coated unit dosage form." Testing the content of metoclopramide HCl should confirm that the metoclopramide in the coating of each **tablet** is between 85% and 115% of the calculated dosage with a standard deviation of no more than 6.4.

DETD Example 6: Examination of **Tablet** Dissolution Time

DETD [0092] Essentially complete solubilization of metoclopramide from the **oral** dosage form was observed within about 5 minutes (using 0.01 M to 0.1 M HCl) for the **tablet** of Example 4.

DETD . . . of a migraine attack with typical symptoms: headache, nausea and sensitivity to light and sound. She is administered a single **oral** (single layer) **tablet** containing metoclopramide (8 mg) and naproxen sodium (250 mg). Her symptoms start to diminish within one hour and, by three. . .

DETD . . . a migraine attack with typical symptoms: migraine headache, nausea and sensitivity to light and sound. She is administered a single **oral** (bilayer) **tablet** containing metoclopramide (16 mg) and naproxen sodium (500 mg). Her symptoms start to diminish within one hour. By three hours,. . .

DETD . . . symptoms as in the patients of Example 7 and 8 are presented by a male, 25 years of age. Upon **oral** administration of a single layer **tablet** containing 16 mg of metoclopramide and 1000 mg naproxen sodium the same result is obtained.

DETD . . . of a migraine attack consisting of typical symptoms: headache, nausea and sensitivity to light and sound. She is administered a **tablet** prepared according to Example 5 containing metoclopramide

(8 mg) and naproxen sodium (500 mg). The naproxen moves from the stomach. . .

DETD . . . shown in Table 2, this was demonstrated based on a comparison of plasma naproxen levels for a single MT 100 **tablet** vs. those for the **tablet** containing naproxen sodium alone. The presence of metoclopramide resulted in an earlier Tmax (by approximately 30 minutes) and a slightly. . .

CLM What is claimed is:

1. A pharmaceutical composition in unit dosage form suitable for **oral** administration in the treatment of migraine headache, comprising: (a) metoclopramide in an amount effective to increase gastric motility in a. . .

2. The pharmaceutical composition of claim 1, wherein said unit dosage form is a **tablet** or capsule.

11. A pharmaceutical composition in unit dosage form suitable for **oral** administration to a human for the treatment of migraine headache, comprising: metoclopramide and an analgesic, present in an amount such. . .

13. The pharmaceutical composition of claim 11, wherein said unit dosage form is a **tablet** or capsule.

. . . The pharmaceutical composition of claim 13, wherein said metoclopramide and said analgesic are each in separate layers of a multilayer **tablet**.

. . . composition of claim 17, wherein said NSAID is selected from the group consisting of: acetaminophen; ibuprofen; flurbiprofen; ketoprofen; naproxen; oxaprozin; **etodolac**; indomethacin; ketorolac; nabumetane; piroxicam; celecoxib; **rofecoxib**; **meloxicam** ; JTE-522; L-745,337; and NS398; or a pharmaceutically acceptable salt thereof.

21. A pharmaceutical composition in unit dosage form suitable for **oral** administration to a human for the treatment of migraine headache, comprising: metoclopramide and an analgesic, present in an amount such. . .

22. The pharmaceutical composition of claim 21, wherein said unit dosage form is a **tablet** or capsule.

. . . 23. The pharmaceutical composition of claim 22, wherein said metoclopramide and said analgesic are in separate layers of a multilayer **tablet**.

. . . composition of claim 25, wherein said NSAID is selected from the group consisting of: acetaminophen; ibuprofen; flurbiprofen; ketoprofen; naproxen; oxaprozin; **etodolac**; indomethacin; ketorolac; nabumetane; piroxicam; celecoxib; **rofecoxib**; **meloxicam**; JTE-522; L-745,337; and NS398; or a pharmaceutically acceptable salt thereof.

. . . pharmaceutical composition of claim 33, wherein said NSAID is selected from the group consisting of: ibuprofen; flurbiprofen; ketoprofen; naproxen; oxaprozin; **etodolac**; indomethacin; ketorolac; nabumetane; piroxicam; celecoxib; **rofecoxib**; **meloxicam**; JTE-522; L-745,337; and NS398; or a pharmaceutically acceptable salt thereof.

37. The pharmaceutical composition of claim 29, wherein said unit dosage form is suitable for **oral** administration.

38. The pharmaceutical composition of claim 37, wherein said unit dosage

form is a **tablet** or capsule.

41. The pharmaceutical composition of claim 29, wherein said unit dosage form is a multilayer **tablet**.

45. The pharmaceutical composition of claim 42, wherein said unit dosage form is suitable for **oral** delivery.

46. The pharmaceutical composition of claim 45, wherein said unit dosage form is a **tablet** or capsule.

. . . The method of claim 55, wherein said NSAID is selected from the group consisting of: ibuprofen; flurbiprofen; ketoprofen; naproxen; oxaprozin; **etodolac**; indomethacin; ketorolac; nabumetane; piroxicam; celecoxib; **rofecoxib**; **meloxicam**; JTE-522; L-745,337; and NS398; or a pharmaceutically acceptable salt thereof.

. . . method of claim 63, wherein said NSAID is selected from the group consisting of: acetaminophen; ibuprofen; flurbiprofen; ketoprofen; naproxen; oxaprozin; **etodolac**; indomethacin; ketorolac; nabumetane; piroxicam; celecoxib; **rofecoxib**; **meloxicam** ; JTE-522; L-745,337; and NS398; or a pharmaceutically acceptable salt thereof.

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TI **Rapid**-melt compositions methods of making same and methods of using same

AB A novel **rapid**-melt composition, including methods of making the same, and methods of using the same for the delivery of prophylactic and therapeutic active materials to a mammal. The **rapid**-melt compositions are formed by molding or compression, with an additional heating step being preferred.

SUMM [0002] The present invention relates to a **rapid**-melt composition for delivery of prophylactic and therapeutic active materials to a mammal, methods of making the same, and methods of. . .

SUMM . . . may be produced in a variety of dosage forms, depending upon the desired route of administration of the therapeutic material. **Oral** dosage forms, for example, include such solid compositions as tablets, emulsions, and suspensions. The particular dosage form utilized will depend. . .

SUMM [0005] **Tablet** compositions offer many advantages, including ease of product handling, chemical and physical stability, portability (in particular, allowing ready availability to. . . as disorders of the upper gastrointestinal tract, wherein delivery of an active material dissolved or dispersed in a liquid ensures **rapid** and complete delivery to the afflicted area. In an effort to obtain the therapeutic advantages associated with liquid formulations as well as the broad advantages associated with solids, many chewable **tablet** formulations have been developed.

SUMM . . . to be chewed either to provide proper flavor or to increase the surface area of a particular drug to permit **rapid** activity in the digestive tract or circulatory systems. However, many pharmaceutical ingredients usually have both an unpleasant mouth feel and. . .

SUMM [0007] Khankari et al., U.S. Pat. No. 6,024,981, discloses a rapidly dissolving robust dosage form directed to a hard **tablet** that can be packaged, stored and processed in bulk. The solid **tablet** dissolves in the mouth of a patient with a minimum of grit. The **tablet** contains an active ingredient mixed into a matrix of a non-direct compression filler and a relatively high lubricant content.

SUMM [0008] Amselem, U.S. Pat. No. 5,989,583, discloses a dry solid lipid composition suitable as an **oral** dosage form. The composition

contains a lipophilic substance, at least one fat which is a solid at about 25.degree. C.. . .

SUMM . . . Nakamichi et al., U.S. Pat. No. 5,837,285, discloses fast soluble tablets that can be produced by a simple method. The **tablet** base is a sugar alcohol. The mixture of the sugar alcohol and a drug is subjected to compressive shaping prior to drying in the process. The dry solid **tablet** can be produced by modification of conventional tableting technology and possesses physico-chemical stability.

SUMM [0012] Chavkin et al., U.S. Pat. No. 5,753,255 discloses a chewable medicinal **tablet**. The **tablet** contains about 30 to about 95% by weight of a capric triglyceride and a medicinally active ingredient up to 60%. . .

SUMM [0013] Geyer et al., U.S. Pat. No. 5,320,848, discloses a nonaqueous chewable composition for **oral** delivery of unpalatable drugs. The drug is intimately dispersed or dissolved in a pharmaceutically-acceptable lipid that is solid at room. . .

SUMM [0014] Lapidus, U.S. Pat. No. 4,937,076, discloses a chewable aspirin and buffering material **tablet** in a single dosage form. The buffering materials are integrally dispersed and bound in a fatty material of chocolate, synthetic. . .

SUMM . . . tablets have a harder outer shell which inhibits penetration of liquid, and a softer interior which quickly liquefies when the **tablet** and shell are broken into pieces and contacted by the liquid. The excipient or base material of the **tablet** is made from carbohydrates held together with small quantities of a carbohydrate binder such as maltodextrin. The tablets can contain. . .

SUMM [0016] Morris et al., U.S. Pat. No. 4,609,543, discloses a soft homogeneous antacid **tablet**. The **tablet** contains solid antacid particles thoroughly coated with a mixture composed of a fatty material or oil, a surfactant, and a. . .

SUMM . . . No. 4,446,135, discloses chewable calcium carbonate-containing antacid tablets having good mouth feel properties. The good mouth feel properties of the **tablet** are obtained by using calcium carbonate of a particular particle size in combination with certain excipients. The calcium carbonate is. . .

SUMM [0018] Puglia et al., U.S. Pat. No. 4,327,077, discloses a compressed chewable antacid **tablet** which has good flexibility, is breakage resistant and disintegrates immediately upon chewing. The **tablet** is formed of a recrystallized fatty material, such as chocolate, a bulking material and an active ingredient bound up in. . .

SUMM [0019] Puglia et al., U.S. Pat. No. 4,327,076, also discloses a compressed chewable antacid **tablet** which has good flexibility, is breakage resistant and disintegrates immediately upon chewing. The **tablet** is formed of particles of the antacid or other active ingredient which are admixed with particles formed of edible fat or oil absorbed on a fat-absorbing material, such as microcrystalline **cellulose**. Upon chewing, the **tablet** is quickly converted to a smooth creamy non-gritty palatable emulsion.

SUMM . . . less palatable after ingestion of multiple doses. Further, the binders and other materials used in such chewable tablets may prevent **rapid** and effective delivery of active materials to the stomach.

SUMM [0021] There is a need for a **rapid**-melt, composition that behaves like a liquid when consumed by a mammal, and yet acts like a solid in many other. . .

SUMM [0023] Applicant has unexpectedly developed a method of preparing a **rapid**-melt composition comprising the steps of:

SUMM [0027] d) compressing said compressible mixture into said **rapid** -melt composition.

SUMM [0028] Applicant has further developed a method of preparing a **rapid**-melt composition comprising the steps of:

SUMM [0032] d) compressing said compressible mixture into said **rapid**-melt composition;

SUMM [0033] e) heating said **rapid**-melt composition to a temperature 40 to 60.degree. C. for a period of 1 to 10 minutes in order to convert. . .

SUMM [0034] f) cooling said heated **rapid**-melt composition.

SUMM [0035] Further, Applicant has unexpected developed a method for preparing a compressed **rapid**-melt composition comprising the steps of:

SUMM [0039] d) compressing said compressible mixture into said **rapid**-melt composition.

SUMM [0040] The **rapid**-melt, semi-solid molded compositions of the present inventive subject matter exhibit good resistence to prolonged exposure to heat and the atmosphere. More particularly, the compositions surprisingly maintain their texture and **rapid** melting properties when exposed to those elements.

SUMM [0041] The **rapid**-melt compositions of the present inventive subject matter contains at least one binder, a salivating agent, an active material, and a diluent/bulking material. The **rapid**-melt compositions may also contain a slipping agent to aid in the transport of the composition from the mouth of the. . .

SUMM . . . liquefication of the compositions. A further way for the composition to be liquified is by the patient sucking on the **rapid**-melt, compositions of the inventive subject matter.

SUMM [0046] The **rapid**-melt technology of the present inventive subject matter has multiple applications which are ideal for the unique properties of the compositions.. . .

SUMM [0050] The **rapid**-melt compositions of the present inventive subject matter are preferably anhydrous, that is, they do not contain any water. The lack. . .

SUMM [0051] The **rapid**-melt compositions of the present inventive subject matter contain at least one binder. As used herein, "binder" means at least one. . .

SUMM [0054] The amount of binder present in the **rapid**-melt composition of the present inventive subject matter is from about 0.01% to about 70% by weight of the final composition.. . .

SUMM [0056] The **rapid**-melt composition of the present inventive subject matter also contains a salivating agent. As is used herein, "salivating agent" means a. . .

SUMM [0059] The amount of salivating agent present in the **rapid**-melt, semi-solid molded composition of the present inventive subject matter is from about 0.05% to about 15% by weight of the. . .

SUMM [0061] The **rapid**-melt compositions of the present inventive subject matter further contain a diluent/bulking material. The use of a diluent/bulking material is necessary. . . lactose, sucrose, sorbitol, fructose, talc, stearic acid, magnesium stearate, dicalcium phosphate, erythitol, xylitol, mannitol, maltitol, isomalt, dextrose, maltose, lactose, microcrystalline **celluloses** and mixtures thereof.

SUMM [0062] The amount of diluent/bulking material present in the **rapid**-melt compositions is from about 10% to about 90% by weight of the final composition. Preferably, the amount of diluent/bulking material. . .

SUMM [0063] The **rapid**-melt compositions of the present inventive subject matter may optionally contain a further slipping agent to aid in the palatability of. . .

SUMM . . . response modifiers, pyrimidine synthesis inhibitors and hyaluronic acid. Specific examples of osteoarthritis and rheumatoid arthritis therapeutics include celecoxib, diclofenac sodium, **rofecoxib**, nabumetone, diclofenac sodium and misoprostol, oxaprozin, **meloxicam**, piroxicam, **etodolac**, naproxen, hylan G-F 20, leflunomide, tenoxicam, and naproxen sodium.

SUMM . . . to mask the unpalatability of the active materials is also well-known. Thus, other materials which can be incorporated into the **rapid**-melt composition of the present inventive subject matter include flavors, colors and sweeteners. A distinct feature of the inventive **rapid**-melt, compositions is that they exhibit excellent taste characteristics. Importantly, it is possible to incorporate high levels of flavors, sweeteners and. . .

SUMM [0101] The **rapid**-melt compositions of the present inventive subject matter may also be coated in order to facilitate handling of the compositions. Coatings. . .

SUMM [0102] The present inventive subject matter also contemplates a method of preparing a **rapid**-melt composition. A preferred method involves the steps of: melting at least one binder having a melting point about 25 to. . .

SUMM [0105] In a preferred embodiment, the **rapid**-melt products of the present inventive subject matter are formed via compression of the ingredients. The compression of the ingredients into **rapid**-melt products may take place in a conventional compression or tableting machine such as a punch and die machine. In addition,. . .

SUMM [0107] The binders present in the inventive **rapid**-melt formulations provide proper binding for the components of the formulation when formed by compression, thus no additional binders or other. . .

SUMM [0108] In a particularly preferred embodiment, after the inventive **rapid**-melt product has been compressed, the compressed product is exposed to an elevated temperature. The conventional way to expose the compressed **rapid**-melt product is to employ a conveyor belt on which the compressed **rapid**-melt product is placed. The conveyor belt then passes through a heating zone, in which heat or hot air is applied to the compressed **rapid**-melt product. The interior of the compressed product is preferably not heated as much as the exterior of the compressed product.. . . product to a temperature of 40 to 60.degree. C. for a period of 1 to 10 minutes. Preferably, the compressed **rapid**-melt product is heated to a temperature of 45 to 55.degree. C. for a period of 2 to 5 minutes.

SUMM [0109] Conventional processes may be employed in order to heat the compressed **rapid**-melt products, with such conventional processes including, but not limited to, a conventional oven, a high voltage heat lamp, a microwave. . .

SUMM . . . in the compressed product. In this way, the fats and emulsifiers which may be considered weak binders when the compressed **rapid**-melt product is first granulated and compressed, the fats and emulsifiers now become a much stronger bonding system.

SUMM [0112] One physical characteristic of the compressed **rapid**-melt product that is changed due to the bonding of the particles by the melted fat/emulsifier system is the friability of the compressed product. Due to the relatively weak binding characteristics of the fats and emulsifiers, the compressed **rapid**-melt product may be friable when first compressed. By surface heating the product and converting the binding system to a bonding. . . system, the compressed product has a much higher integrity which allows it to be easily packaged. In other words, the **tablet**'s friability has decreased significantly from very high to almost nothing. The **tablet** has a high integrity that is suitable for packaging in any form, including large bottles, and the stability of the. . .

SUMM [0113] In a further preferred embodiment of the present inventive subject matter, the active ingredient is added to the compressed **rapid**-melt composition during the lubrication step of the process. That is, the active ingredient is added to the mixture at the. . .

SUMM [0115] As stated previously, it is an important aspect of the present inventive subject matter that the compressed **rapid**-melt

product disintegrates quickly in the mouth of the mammal. Preferably, the compressed **rapid**-melt product disintegrates in less than 20 seconds of being placed in the mammal's mouth, preferably within 10 seconds, and more. . .

SUMM . . . the compressed product. The bonding agent does so by helping reduce the porosity, i.e. increase the density, in the compressed **rapid**-melt product and creating close bonds between the particles in the compressed **rapid**-melt products.

SUMM [0120] Optionally, the compressed **rapid**-melt products prepared by this embodiment may be subjected to a heat treatment to further enhance the bonding as is discussed above. In particular, the compressed product is exposed to an elevated temperature. The conventional way to expose the compressed **rapid**-melt product is to employ a conveyor belt on which the compressed **rapid**-melt product is placed. The conveyor belt then passes through a heating zone, in which heat or hot air is applied to the compressed **rapid**-melt product. The heat or hot air heats the product to a temperature of 40 to 60.degree. C. for a period of 1 to 10 minutes. Preferably, the compressed **rapid**-melt product is heated to a temperature of 45 to 55.degree. C. for a period of 2 to 5 minutes.

SUMM [0121] Conventional processes may be employed in order to heat the compressed **rapid**-melt products, with such conventional processes including, but not limited to, a conventional oven, a high voltage heat lamp, a microwave. . .

SUMM . . . bonding system between the particles in the compressed product. Whereas the fats and emulsifiers are weak binders when the compressed **rapid**-melt product is first granulated and compressed, the fats and emulsifiers now become a much stronger bonding system.

SUMM [0125] The **rapid**-melt compositions of the present inventive subject matter produced by the above methods have increased product integrity and stability. The compositions. . .

DETD Preparation of Compressed **Rapid**-Melt Product Containing Chondroitin and Glucosamine

DETD Preparation of Compressed **Rapid**-Melt Product Containing Glucosamine

DETD Preparation of Compressed **Rapid**-Melt Product Containing Calcium

DETD Preparation of **Cellulose**-Containing Compressed **Rapid** -Melt Product with a Bonding Agent

DETD . . . mixed well and set aside until free from lumps. In the meantime, 73.40% mannitol powder was blended with 24.6% microcrystalline **cellulose** and 0.21% color agents. After mixing an appropriate time, the gum solution was added to the mixture in small amounts.. . .

DETD Preparation of Bonded **Rapid**-Melt Product

DETD [0141] Mannitol granules were prepared by mixing 89.00% mannitol with 10.00% microcrystalline **cellulose**. The mannitol and microcrystalline **cellulose** were granulated with 1.00% polyvinyl pyrrolidone.

DETD Preparation of Bonded **Rapid**-Melt Product

DETD [0144] Mannitol granules were prepared by mixing 89.00% mannitol with 10.00% microcrystalline **cellulose**. The mannitol and microcrystalline **cellulose** were granulated with 1.00% polyvinyl pyrrolidone.

DETD Preparation of a Non-Bonded **Rapid**-Melt Product

DETD [0147] Mannitol granules were prepared by mixing 89.00% mannitol with 10.00% microcrystalline **cellulose**. The mannitol and microcrystalline **cellulose** were granulated with 1.00% polyvinyl pyrrolidone.

CLM What is claimed is:

1. A method of preparing a **rapid**-melt composition comprising the steps of: a) melting at least one binder in an amount from about 0.01% to about 70%. . . said first mixture with said second mixture

to form a compressible mixture; and d) compressing said compressible mixture into said **rapid**-melt composition.

10. The method according to claim 1 further comprising the step of heating said **rapid**-melt composition to a temperature of 40 to 60.degree. C. for a period of 1 to 10 minutes.

11. A method of preparing a **rapid**-melt composition comprising the steps of: a) melting at least one binder in an amount from about 0.01% to about 70%. . . . combining said first mixture with said second mixture to form a compressible mixture; d) compressing said compressible mixture into said **rapid**-melt composition; e) heating said **rapid**-melt composition to a temperature 40 to 60.degree. C. for a period of 1 to 10 minutes in order to convert said binder to a bonding agent; and f) cooling said heated **rapid** -melt composition.

12. The method according to claim 11 wherein said heating step is carried out by heating said **rapid**-melt composition to a temperature of 45 to 55.degree. C.

14. The method according to claim 11 wherein said heating step is carried out by heating said **rapid**-melt composition to a temperature of 45 to 55.degree. C. for 2 to 5 minutes.

23. A method for preparing a compressed **rapid**-melt composition comprising the steps of: a) mixing at least one diluent present in an amount of 0.1 to 70% by. . . amount of 5 to 30% by weight to form a compressible mixture; and d) compressing said compressible mixture into said **rapid**-melt composition.

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SUMM . . . typically: aspirin, 500-650 mg; acetaminophen, 500 mg; naproxen sodium, 750-825 mg; tolfenamic acid, 200-400 mg; and, ibuprofen 200 mg. After **oral** dosing, peak plasma concentrations in normal subjects usually occur at about 1 hour for aspirin and acetaminophen, and between 1. . .

SUMM Metoclopramide is a drug known to relieve migraine-associated nausea when administered at a minimum **oral** dose of 10 mg. Poyser et al. have described a formulation in which aspirin is uniformly intermixed with metoclopramide (U.S.. . .

SUMM In its first aspect, the present invention is directed to a pharmaceutical composition in unit dosage form suitable for **oral** administration in the treatment of migraine headache. The dosage form contains metoclopramide in an amount effective to increase gastric motility. . . non-acidic NSAID) in an amount effective to reduce or eliminate headache pain. Preferably, the dosage form should be either a **tablet** or capsule and should be free from vasoactive agents, including 5 HT agonist vasoactive agents. The dosage form may be. . .

SUMM . . . which either metoclopramide or analgesic is barrier coated. Alternatively, metoclopramide and analgesic may be in separate layers of a multilayer **tablet**. Dosage forms should typically be free of vasoactive agents, may be coordinated and may contain either long-acting NSAIDs or NSAIDs formulated to be long acting. Typical NSAIDs that may be used include: acetaminophen; ibuprofen; flurbiprofen; ketoprofen; naproxen; oxaprozin; **etodolac**; indomethacin; ketorolac; nabumetane; piroxicam; celecoxib; **rofecoxib**; **meloxicam** ; JTE-522; L-745,337; NS398; and pharmaceutically acceptable salts thereof. The most preferred analgesic is naproxen. This should be present at between. . .

SUMM . . . reduce or eliminate headache pain. Long acting NSAIDs suitable

for use in the dosage forms include: ibuprofen; flurbiprofen; ketoprofen; oxaprozin; **etodolac**; indomethacin; ketorolac; nabumetane; piroxicam; celecoxib; **rofecoxib**; **meloxicam** ; JTE-522; L-745,337; NS398; or pharmaceutically acceptable salts thereof When naproxen, the preferred analgesic, is used, it should be present in. . . of Controlled Drug Delivery, Edith Mathiowitz, John Wiley & Sons (1999), ISBN: 0471148288). Coordinated dosage forms should be suitable for **oral** delivery and will typically take the form of a **tablet** or capsule. Metoclopramide and NSAID may be in separate layers of a multilayer **tablet** and, in general, these dosage forms should be substantially free of vasoactive agents such a 5 HT agonists.

SUMM . . . or NSAIDs formulated to be long acting) may be acid-base storage stabilized or coordinated and should, preferably, be suitable for **oral** administration (e.g. in the form of a **tablet** of capsule). It will also generally be advantageous for metoclopramide to be present at a concentration effective to reduce or. . .

SUMM . . . the method. NSAIDS that can be used include: acetaminophen (when formulated to be long acting); ibuprofen; flurbiprofen; ketoprofen; naproxen; oxaprozin; **etodolac**; indomethacin; ketorolac; nabumetane; piroxicam; celecoxib; **rofecoxib**; **meloxicam**; JTE-522; L-745,337; NS398; or pharmaceutically acceptable salts thereof In general, naproxen is the most preferred NSAID, particularly when in the. . .

DRWD FIG. 4. is a comparative dissolution plot of the metoclopramide presented in a **tablet** coating layer and presented in a compressed **tablet** layer.

DRWD FIG. 5a is a plot of plasma concentrations of metoclopramide upon administration of **tablet**(s) of the present invention as disclosed in **Tablet** Example 4.

DRWD FIG. 5b is a plot of plasma concentrations of naproxen sodium upon administration of **tablet**(s) of the present invention as disclosed in **Tablet** Example 4.

DRWD FIG. 6 is a diagrammatic cross section side view of a **tablet** coating pan with baffles and spray nozzles.

DETD . . . that serves as a barrier to prevent interaction or the drugs may be segregated into different layers of a multilayer **tablet** . Methods for producing "acid-base storage stabilized" dosage forms are described in the Examples section below. Such dosage forms may, of. . .

DETD . . . is preferred that formulations for the treatment of patients be free from vasoactive agents and that they be suitable for **oral** administration.

DETD The Making of **Tablet** Dosage Forms

DETD The combination of metoclopramide and an analgesic may take place in a single layer **tablet** or other solid dosage form. A bi- or multi layer **tablet** of the type described in this invention relieves nausea, improves gastrointestinal motility which enhances the speed of absorption of the. . .

DETD In a bilayer configuration, one portion of the **tablet** contains metoclopramide in the required dose and appropriate excipients, agents to aid dissolution, lubricants, fillers, etc., and is, preferably, designed. . . in the stomach in less than about 10 minutes, thus increasing gastrointestinal motility and controlling nausea. The effect of the **rapid** availability of metoclopramide is to accelerate delivery of the naproxen (or other analgesic) to the small intestine which is the site of most **rapid** absorption. In a bilayer **tablet** embodiment, the second portion of the **tablet** will contain, preferably, naproxen sodium in the required dose and appropriate excipients, agents to aid dissolution, lubricants, fillers, etc. It. . .

DETD In one embodiment of bilayer **tablet** preparation, once the two

components have been manufactured, they are combined into a single **tablet**. This process allows for different dosages of either component (i.e. the metoclopramide component or the naproxen sodium component) to be usefully combined into a single **tablet** in an efficient way. In another embodiment, substantially each naproxen sodium crystal (or metoclopramide particle) is coated with a **rapid** dissolving excipient material, conveniently, prior to tableting.

DETD Powder flow characteristics and powder compressibility are the main criteria to be considered with respect to successful **tablet** production. To improve compressibility, naproxen sodium may be granulated. This involves increasing granule size through the addition of excipients that. . .

DETD . . . forms should be used, e.g., the acidic analgesic and the metoclopramide may be sequestered to different layers of a multilayer **tablet** in such a manner that contact between the drugs is eliminated or minimized. In the case of COX-2 inhibitors, the. . . when contained in tablets of from about 100 to 200 mg. Celecoxib peak plasma concentrations occur approximately 3 hours after **oral** dosing. The effective half-life is approximately 11 hours.

DETD . . . to 15 hours and about 12 to 13 hours respectively; oxaprozin with a half-life of about 42 to 50 hours; **etodolac** with a half-life of about 7 hours; indomethacin with a half-life of about 4 to 6 hours; ketorolac with a. . .

DETD . . . those skilled in the art. It is to be further understood that drug dosages are, in particular instances, measured as **oral** dosages, or parenteral or inhaled dosages or with reference to drug levels as measured in blood.

DETD . . . at least 10 mg by injection i.m. or intravenously to be useful for the treatment of the nausea accompanying migraine. **Oral** doses of 10-20 mg are less useful because it takes longer for therapeutic blood levels to be reached, resulting in. . .

DETD . . . a range of from about 25 to 75 mg, when present in suppositories at about 50 mg, and when in **oral** suspensions at a concentration of about 25 mg/5 ml. A typical daily **oral** dosage of indomethacin is three 25 mg doses taken at intervals during one day. However, daily doses of up to. . .

DETD Naproxen is particularly useful when contained in tablets of from 250 to 500 mg, and in **oral** suspensions of about 125 mg/5 ml. For naproxen sodium, tablets of about 275 or about 550 mg are particularly useful.. . .

DETD **Etodolac** is usefully provided in capsules of 200 mg and 300 mg and in tablets of 400 mg. Useful doses for. . .

DETD . . . tablets of 10 mg and as a sterile parenteral preparation for injection in 15 mg/ml and 30 mg/ml dosage forms. **Oral** doses of up to 40 mg, and particularly 10-30 mg per day and parenteral doses up to 120-150 mg per. . .

DETD One particular group of long acting NSAIDs that may be used are the cyclooxygenase-2 ("COX-2") inhibitors, for example: celecoxib, **rofecoxib**, **meloxicam**, piroxicam, JTE-522, L-745,337, or NS398, or pharmaceutically acceptable salts thereof. JTE-522, L-745,337 and NS398 are described, inter alia, in Wakitani,. . . al., Jpn. J. Pharmacol. 78:365-371 (1998); and Panara, et al., Br. J. Pharmacol. 116:2429-2434 (1995). The amount present in a **tablet** or administered to a patient will depend upon the particular COX-2 inhibitor being used. For example, piroxicam may be present at 10 to 20 mg per **tablet**. Celecoxib may be administered to a human in an amount of from about 100 mg to about 500 mg or. . .

DETD . . . an effective local gastrointestinal concentration. In a preferred embodiment of co-timely drug administration, both drugs are administered in a single **oral** unit dosage form.

DETD . . . at about 2 to 4 hours and 1 to 2 hours respectively; oxaprozin peaks at about 3 to 5 hours; **etodolac** peaks at about 1 to 2

hours; indomethacin peaks at about 1 to 4 hours; ketorolac peaks at about one-half. . .

DETD G. "**Rapid** availability" as to metoclopramide in an **oral** dosage form shall be understood to be essentially the complete solubilization of metoclopramide from the dosage form within 30 minutes and preferably within 5 minutes from ingestion. Clearly, an **oral** dosage form of metoclopramide which is liquid at the time of administration would also represent a "**rapid** availability" form.

DETD N. "Unit dosage form" shall mean single drug administration entity. By way of example, a single **tablet**, capsule, dragee, or trochee (**oral** unit dosage forms), suppository, or syringe combining both metoclopramide and an NSAID would be a unit dosage form. Administration of. . .

DETD . . . professional. Maximum daily doses in milligrams is as follows: flurbiprofen 300; ketoprofen 300; naproxen 1500, naproxen sodium 1375; oxaprozin 1800; **etodolac** 1200; indomethacin 150 to 200; ketorolac 120 mg i.m. and 40 **oral**; nabumetane 2000; mefenamic acid 1000; and piroxicam 20.

DETD . . . levels of metoclopramide. The data was obtained from 10 healthy volunteer subjects. On day 1, the subjects were administered one **tablet** of 500 mg naproxen sodium and 8 mg metoclopramide prepared as described in the Examples section. On day 4, two. . .

DETD **Tablet** Formulation #1

DETD A variety of combinations of metoclopramide and analgesic can be made into a single dosage form (e.g., **tablet**, capsule, suppository) consisting of one or more layers. In this example, a sequentially and rapidly dissolving single layer **tablet** of metoclopramide, 8 mg, is combined with naproxen sodium, 500 mg. Referring to FIG. 1, this single layer **tablet** contains naproxen sodium in crystalline form (2) and metoclopramide (4), each uniformly distributed throughout a matrix (6) of pharmaceutically acceptable fillers, excipients, binding agents, disintegrants, and lubricants (collectively, "carrier material"). A pharmaceutically acceptable **tablet** coating (8) surrounds the active ingredients and carrier materials. Carrier material should be present in an amount of between 50 and 2000 mg, and preferably between 500 and 1,000 mg. Prior to compaction in a **tablet**, each crystal of naproxen sodium may optionally be coated with excipient. Tablets may include microcrystalline **cellulose** and magnesium stearate. For example, naproxen sodium may be coated with hydroxypropyl methylcellulose 2910 and polyethylene 8000. A core bulking. . . YS-1-4215 (trademarks of Colorcon, West Point, Pa.). Povidone and talc may also be used as bulking agents for the **tablet** core.

DETD **Tablet** stability is compromised in instances in which there is an "acid-base incompatibility" between the metoclopramide and the analgesic. For example,. . . The basic salt of metoclopramide intimately mixed with acidic naproxen sodium crossreacts in a matter of days causing reduction in **tablet** potency of about 5% in two weeks and about 20 to 25% or more in three weeks at ambient temperature.. . . applied in combination with water for irrigation and talc. Other materials are shellac, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, and **cellulose** acetate phthalate. Thin coatings, on the order of about 25-250 microns, retard the availability of naproxen by no more than. . .

DETD **Tablet** Formulation #2

DETD FIG. 2. depicts a sequentially and rapidly dissolving bilayer **tablet** of metoclopramide, 16 mg, combined with naproxen sodium 500 mg. The **tablet** consists of a first layer (11) and a second layer (13). The first layer (11) contains naproxen sodium in crystalline. . . a matrix (17) of pharmaceutically acceptable fillers, excipients, binding agents, disintegrants, and lubricants (collectively, "second carrier material"). A pharmaceutically acceptable

tablet coating (18) surrounds the active ingredients and carrier materials. Dotted line 15 represents the interface between the two layers which are separately molded, poured, compressed or otherwise formed and joined by compression or other **tablet** forming means. The first carrier material and the second carrier material may be either the same or different.

DETD **Tablet** Formulation #3

DETD A particular example of a **tablet** in which metoclopramide is in an effervescent matrix separated from analgesic is as follows:

DETD B. Naproxen: 500 mg of naproxen sodium are compacted as granules with: povidone k-29/32 (23.6 mg); microcrystalline **cellulose**, NF (105.9 mg); croscarmellose sodium, NF, (13.5 mg); talc (27 mg); and magnesium stearate (5 mg).

DETD C. The metoclopramide granules and the naproxen are combined into a two-layer **tablet** as described in Example 2.

DETD **Tablet** Formulation #4

DETD FIG. 3. depicts another example of a sequentially and rapidly dissolving bilayer **tablet** in which metoclopramide hydrochloride (8 mg) is combined with naproxen sodium (500 mg). Referring to the figure, the bilayer **tablet** consists of a first layer (311) and a second layer (313) having an exterior portion (317) and an interior portion. . . crystalline form (314) uniformly distributed throughout the exterior portion of layer (313), wherein (317) comprises a matrix of pharmaceutically acceptable **tablet** coating. A **tablet** coating (317) surrounds both the second layer as well as the layer of naproxen and carrier material (311). Dotted line. . . interface between the exterior portion (313) and the interior portion (319). This interface may comprise titanium dioxide, camauba wax, shellac, **cellulose** acetate phthalate or the like. Interior portion (319) may comprise about 2 to 3% of the coating material of (313). . .

DETD The naproxen-containing portion of tablets may be separately molded, poured, compressed or otherwise formed and joined by compression or other **tablet** forming means. It is then spray coated with a material absent metoclopramide, e.g., HPMC, triethyl citrate, and TiO2 applied in. . .

DETD Preparation of a **tablet** of FIG. 3 requires particular attention to the application of metoclopramide in such a manner as to maintain acceptable **tablet** dosage uniformity ("uniform-coated unit dosage form"). Coating should be uniform to between 85% and 115% of the intended dosage with. . . deviation of 6.4 or less. With pancoating methodology, it is important to control pan speed, movement of tablets across the **tablet** bed, spray temperature and spray coverage relative to the entire pan. Tablets sticking to each other or to the pan. . .

DETD FIG. 6 depicts an apparatus for coating tablets. A rotating coating pan (602) is partially filled with **tablet** cores to be coated. In the embodiment shown, screen panels (604) facilitate air circulation, and baffles (608) placed on the coating pan walls agitate **tablet** cores during rotation. Spray nozzles ((612) and (614)) leading from a spray mixture reservoir, and pump means spray coating through an inlet (610) over **tablet** cores. An air source (618) introduces drying air into the coating pan from a heating and pumping source (not shown).. . .

DETD . . . Franklin Park Ill.)). Using two spray guns about 10 to 12 inches apart and 4 to 8 inches above the **tablet** bed should produce a suitable coating when pans are rotated at a speed of 14 to 16 rpm. It is particularly important to maintain **tablet** movement in the pan to avoid **tablet** sticking and enhance coating uniformity.

DETD **Tablet** Formulation #5 (Metoclopramide Film Coated **Tablet**)

DETD This acid-base storage stable uniform-coated unit dosage form has

metoclopramide as a film in the outermost portion of the **tablet** and separated from the naproxen sodium. The final **tablet** formulation by weight is as follows:

DETD . . . 0.5%
metoclopramide 26% .+-. 1%
talc 24% .+-. 1%
(ii) metoclopramide free coating
(in percentage of total
tablet dry weight)
hydroxypropylmethylcellulose 9%
titanium dioxide 1%
triethyl citrate 2%
B. naproxen core
naproxen sodium 500 mg
povidone k-29/32 23.6 mg
microcrystalline **cellulose**, NF, 105.9 mg
croscarmellose sodium, NF 13.5
talc 27 mg
magnesium stearate 5 mg

DETD To prepare a two layer **tablet** as in FIG. 3., particular attention is paid to the application of the film coating. Naproxen cores are placed in. . . 14-16 rpm. From two spray guns mounted about 4 to 8 inches apart and 10 to 12 inches above the **tablet** bed, atomized metoclopramide-free coating mixture is sprayed over the rotating pan until the cores increase from about 2% to about. . .

DETD . . . step, tablets are again spray coated in the rotating baffled pan, but now with a metoclopramide-containing coating material until the **tablet** weight increases from about 8 to about 10% over the weight of the naproxen core. For example, sufficient spraying may be performed to apply 8 mg of metoclopramide to each **tablet**.

DETD . . . "uniform-coated unit dosage form." Testing the content of metoclopramide HCl should confirm that the metoclopramide in the coating of each **tablet** is between 85% and 115% of the calculated dosage with a standard deviation of no more than 6.4.

DETD Examination of **Tablet** Dissolution Time

DETD Essentially complete solubilization of metoclopramide from the **oral** dosage form was observed within about 5 minutes (using 0.01 M to 0.1 M HCl) for the **tablet** of Example 4.

DETD . . . of a migraine attack with typical symptoms: headache, nausea and sensitivity to light and sound. She is administered a single **oral** (single layer) **tablet** containing metoclopramide (8 mg) and naproxen sodium (250 mg). Her symptoms start to diminish within one hour and, by three. . .

DETD . . . a migraine attack with typical symptoms: migraine headache, nausea and sensitivity to light and sound. She is administered a single **oral** (bilayer) **tablet** containing metoclopramide (16 mg) and naproxen sodium (500 mg). Her symptoms start to diminish within one hour. By three hours,. . .

DETD . . . symptoms as in the patients of Example 7 and 8 are presented by a male, 25 years of age. Upon **oral** administration of a single layer **tablet** containing 16 mg of metoclopramide and 1000 mg naproxen sodium the same result is obtained.

DETD . . . of a migraine attack consisting of typical symptoms: headache, nausea and sensitivity to light and sound. She is administered a **tablet** prepared according to Example 5 containing metoclopramide (8 mg) and naproxen sodium (500 mg). The naproxen moves from the stomach. . .

DETD . . . shown in Table 2, this was demonstrated based on a comparison of plasma naproxen levels for a single MT 100 **tablet** vs. those for the **tablet** containing naproxen sodium alone. The presence of metoclopramide resulted in an earlier Tmax (by approximately 30 minutes) and a slightly. . .

CLM What is claimed is:

1. A pharmaceutical composition in unit dosage form suitable for **oral** administration in the treatment of migraine headache, comprising; (a) metoclopramide in an amount effective to increase gastric motility in a. . .

2. A pharmaceutical composition in unit dosage form suitable for **oral** administration in the treatment of migraine headache, comprising: (a) metoclopramide in an amount effective to increase gastric motility in a. . .

5. A pharmaceutical composition in unit dosage form suitable for **oral** administration to a human for the treatment of migraine headache, comprising: metoclopramide and naproxen, present in an amount such that. . .

6. A pharmaceutical composition in unit dosage form suitable for **oral** administration to a human for the treatment of migraine headache, comprising: metoclopramide and an analgesic, present in an amount such. . .

7. The pharmaceutical composition of claim 6, wherein said unit dosage form is a **tablet** or capsule.

. . . 8. The pharmaceutical composition of claim 7, wherein said metoclopramide and said analgesic are in separate layers of a multilayer **tablet**.

. . . composition of claim 10, wherein said NSAID is selected from the group consisting of: acetaminophen; ibuprofen; flurbiprofen; ketoprofen; naproxen; oxaprozin; **etodolac**; indomethacin; ketorolac; nabumetane; piroxicam; celecoxib; **rofecoxib**; **meloxicam** ; JTE-522; L-745,337; and NS398; or a pharmaceutically acceptable salt thereof.

. . . method of claim 18, wherein said NSAID is selected from the group consisting of: acetaminophen; ibuprofen; flurbiprofen; ketoprofen; naproxen; oxaprozin; **etodolac**; indomethacin; ketorolac; nabumetane; piroxicam; celecoxib; **rofecoxib**; **meloxicam** ; JTE-522; L-745,337; and NS398; or a pharmaceutically acceptable salt thereof.

22. A pharmaceutical composition in unit dosage form suitable for **oral** administration in the treatment of migraine headache, comprising: (a) metoclopramide in an amount effective to increase gastric motility in a. . .

23. The pharmaceutical composition of claim 22, wherein said unit dosage form is a **tablet** or capsule.

30. A pharmaceutical composition in unit dosage form suitable for **oral** administration in the treatment of migraine headache, comprising: (a) metoclopramide in an amount effective to increase gastric motility in a. . .

32. The pharmaceutical composition of either claim 30 or claim 31, wherein said unit dosage form is a **tablet** or capsule.

34. A pharmaceutical composition in unit dosage form suitable for **oral** administration to a human for the treatment of migraine headache, comprising: metoclopramide and an analgesic, present in an amount such. . . acid-base storage stabilized dosage form in which said metoclopramide and said analgesic are each in separate layers of a multilayer **tablet**.

35. A pharmaceutical composition in unit dosage form suitable for **oral** administration to a human for the treatment of migraine headache, comprising: metoclopramide and an analgesic, present in an

amount such. . .

. . . composition of claim 38, wherein said NSAID is selected from the group consisting of: acetaminophen; ibuprofen; flurbiprofen; ketoprofen; naproxen; oxaprozin; **etodolac**; indomethacin; ketorolac; nabumetane; piroxicam; celecoxib; **rofecoxib**; **meloxicam** ; JTE-522; L-745,337; and NS398; or a pharmaceutically acceptable salt thereof.

L6 ANSWER 7 OF 11 USPATFULL on STN

SUMM . . . passageway in the wall communicates the active agent layer with the environment of use. The patent describes the use of **cellulose** acylate as the material comprising the semipermeable membrane.

SUMM . . . the combined mechanisms of diffusion and osmotic pumping. These patents also disclose the formation of asymmetric membranes with 398-10 (Eastman) **cellulose** acetate.

SUMM . . . permeable membrane alone, however, does not allow the inclusion of a low molecular weight osmotic agent in the pharmaceutical composition **tablet** core (for example, potassium chloride, sodium tartrate, sodium chloride, sodium sulfate, etc.). Thus, it limits the versatility of the device. . . of the devices requires the use of sophisticated and expensive electronic equipment able to recognize the different layers of the **tablet** core.

SUMM [0023] c) a membrane immediately surrounding the composition and comprising a mixture of a **cellulose** acylate (ester), a methacrylate salt copolymer and a plasticizer, wherein the membrane permits delivery of the at least one active. . .

SUMM . . . micropores for delivery of the at least one active agent by diffusion, and the membrane further comprising one or more **cellulose** esters, one or more poly(methacrylate) copolymer salts and one or more plasticizers,

SUMM . . . comprises a drug-containing coat external to the membrane, wherein the drug-containing coat comprises a second active agent, provides an immediate, **rapid**, controlled and/or delayed release of the second active agent and the external coat surrounds at least a portion of the. . . second active agents are the same; 16) the membrane comprises about 1 to 99 weight percent of one or more **cellulose** esters, about 84 to 0.5 weight percent of one or more poly(methacrylate) copolymer salts and about 15 to 0.5 weight percent of one or more plasticizers; 17) the **cellulose** ester is selected form the group consisting of **cellulose** acylate, **cellulose** diacylate, **cellulose** triacylate, **cellulose** acetate, **cellulose** diacetate, **cellulose** triacetate and combinations thereof; 18) the poly(methacrylate) copolymer salt is poly(ammonium methacrylate) copolymer; 19) the layer further comprises at least. . . polymer is one or more of hydroxypropyl methylcellulose, alkylcellulose, hydroxyalkylcellulose, poly(alkylene oxide), and combinations thereof; and the at least one **cellulose** ester is independently selected from the group consisting of **cellulose** acylate, **cellulose** diacylate, **cellulose** triacylate, **cellulose** acetate, **cellulose** diacetate, **cellulose** triacetate and combinations thereof; 21) the core excludes an active agent; 22) the membrane comprises a mixture of a **cellulose** acylate, a poly(methacrylate) copolymer salt and a plasticizer; 23) a slightly soluble or insoluble active substance is delivered predominantly through. . .

SUMM [0033] Other preferred embodiments of the device of the invention are used in biological environments including the **oral**, ocular, nasal, vaginal, glandular, gastrointestinal tract, rectal, cervical, intrauterine, arterial, venous, otic, sublingual, dermal, epidermal,

subdermal, implant, buccal, bioadhesive, mucosal. . .

DRWD [0036] FIG. 1-a is a sectional view of an **oral** device according to the present invention.

DETD [0039] FIG. 1-a depicts an **oral** dosage form device (1) comprising an approximately centrally located core (2) comprising an expandable hydrophilic polymer composition capable of absorbing,. . .

DETD . . . an osmopolymer, and an osmagent. The wall surrounding and in contact with the layer containing active agent can comprise a **cellulose** ester, such as **cellulose** acetate, **cellulose** propionate, and **cellulose** acetate-butyrate, a polymethacrylate copolymer, such as poly(ammonium methacrylate) copolymer and (ethyl acrylate)-(methyl methacrylate)-[(trimethylammonium)ethyl methacrylate], and a plasticizer, such as PEG 400, PEG 6000, triacetin and glycerin. The **cellulose** ester, polymethacrylate copolymer and plasticizer are generally present in the ratio of 0.1-99.8 wt. **cellulose** ester: 0.1-99.8% wt. polymethacrylate copolymer: 0.1-25% plasticizer. For very water soluble active agents, such as meperidine HCl, buspirone HCl, diltiazem. . . expandable polymer and an osmagent. The wall surrounding and in contact with the layer containing active substance generally comprise a **cellulose** ester, a poly(methacrylate) copolymer, and a plasticizer.

DETD . . . an osmopolymer and an osmagent. The wall surrounding and in contact with the layer containing active agent can comprise a **cellulose** ester, a polymethacrylate copolymer, and a plasticizer. The **cellulose** ester, polymethacrylate copolymer and plasticizer are generally present in the ratio of 0.1-99.8% wt. **cellulose** ester:0.1-99.8% wt. polymethacrylate copolymer:0.1-25% plasticizer.

DETD [0052] The membrane, or wall, (4) according to the invention preferably comprises a mixture of **cellulose** esters (CE), copolymers of methacrylate salts (CM) and a plasticizer (P). The active agent is released in a controlled manner. . .

DETD [0053] Representative **cellulose** esters useful in the membrane of the invention include **cellulose** acylate; mono, di and tricellulose alkanylates; mono, di and tricellulose aroylates; **cellulose** propionate; **cellulose** acetate-butyrate; **cellulose** triacylates such as **cellulose** trivalerate, **cellulose** trilaurate, **cellulose** tripalmitate, **cellulose** trisuccinate; **cellulose** diacylates such as **cellulose** disuccinate, **cellulose** dipalmitate; combinations thereof and other **cellulose** esters used by those of ordinary skill in the art in the preparation of controlled delivery devices and membranes.

DETD [0060] The device of the present invention can, optionally, include an external coating comprising an active agent for immediate, **rapid**, slow, sustained, extended, controlled or delayed delivery to the environment of use. Useful materials for the external coating include poly(vinylpyrrolidone) (PVP), poly(ethylene glycol) (PEG), hydroxypropyl ethylcellulose, hydroxypropyl methylcellulose, ethylcellulose, hydroxyethylcellulose, sodium carboxymethyl **cellulose**, dimethylaminoethyl methalcrylate-methalcrylate acid ester copolymer, soluble polysaccharide gums such as carrageenan, tragacanth, pectin, guar, combinations thereof and other such materials. . .

DETD . . . comprise adsorbents, acidifying agents, alkalizing agents, antioxidants, buffering agents, colorants, flavorants, sweetening agents, antiadherents, binders, diluents, direct compression excipients, disintegrants, **tablet** glidants, **tablet** or capsule opaquants and/or **tablet** polishing agents.

DETD [0072] As used herein, the expression "antiadherents" is intended to mean agents that prevent the sticking of **tablet** formulation ingredients to the punches and dies in a tableting machine during

production. Such compounds include, by way of example. . .

DETD [0073] As used herein, the term "binders" is intended to mean substances used to cause adhesion of powder particles in **tablet** granulations. Such compounds include, by way of example and without limitation, acacia, alginic acid, tragacanth, carboxymethylcellulose sodium, poly (vinylpyrrolidone), compressible. . .

DETD . . . Exemplary binders include starch, poly(ethylene glycol), guar gum, polysaccharide, bentonites, sugars, invert sugars, poloxamers (PLURONIC.TM. F68, PLURONIC.TM. F127), collagen, albumin, **celluloses** in nonaqueous solvents, combinations thereof and the like. Other binders include, for example, poly(propylene glycol), polyoxyethylene-polypropylene copolymer, polyethylene ester, polyethylene sorbitan ester, poly(ethylene oxide), microcrystalline **cellulose**, poly(vinylpyrrolidone), combinations thereof and and other such materials known to those of ordinary skill in the art.

DETD . . . tablets and capsules. Such compounds include, by way of example and without limitation, dibasic calcium phosphate, kaolin, sucrose, mannitol, microcrystalline **cellulose**, powdered **cellulose**, precipitated calcium carbonate, sorbitol, starch, combinations thereof and other such materials known to those of ordinary skill in the art.

DETD [0076] As used herein, the term "**tablet** direct compression excipient" is intended to mean a compound used in direct compression **tablet** formulations. Such compounds include, by way of example and without limitation, dibasic calcium phosphate (e.g. Ditab.TM.), microcrystalline **cellulose**, direct compression lactose (e.g. Tablettose.TM., Lactose DT) combinations thereof and other such materials known to those of ordinary skill in. . .

DETD [0077] As used herein, the term "glidant" is intended to mean agents used in **tablet** and capsule formulations to improve flow-properties during **tablet** compression and to produce an anti caking effect. Such compounds include, by way of example and without limitation, colloidal silica,. . .

DETD [0078] As used herein, the term "lubricant" is intended to mean substances used in **tablet** formulations to reduce friction during **tablet** compression. Such compounds include, by way of example and without limitation, calcium stearate, magnesium stearate, mineral oil, stearic acid, zinc. . .

DETD [0079] As used herein, the term "**tablet**/capsule opaquant" is intended to mean a compound used to used in **tablet** coatings or capsules providing useful opacity which can aid the stability to the light in case of sensitive agents. It. . .

DETD [0080] As used herein, the term "**tablet** polishing agent" is intended to mean a compound used to impart brightness to the surface of the coated tablets. Such. . .

DETD [0081] As used herein, the term "**tablet** disintegrant" is intended to mean a compound used in solid dosage forms to promote the disruption of the solid mass. . . without limitation, starches such as corn starch, potato starch, pre-gelatinized and modified starches thereof, sweeteners, clays, such as bentonite, microcrystalline **cellulose** (e.g. Avicel.TM.), carboxymethylcellulose calcium, **cellulose** polyacrylin potassium (e.g. Amberlite.TM.), alginates, sodium starch glycolate, gums such as agar, guar, locust bean, karaya, pectin, tragacanth, combinations thereof. . .

DETD . . . provide a device with a desired release profile. Such components include, by way of example and without limitation, glycerylmonostearate, nylon, **cellulose** acetate butyrate, d,l-poly (lactic acid), 1,6-hexanediamine, diethylenetriamine, starches, derivatized starches, acetylated monoglycerides, gelatin coacervates, poly(styrene-maleic acid) copolymer, glycowax, castor wax,. . .

DETD [0094] Representative anti-inflammatory and analgesic drugs include cortisone, hydrocortisone, prednisone, prednisolone, betamethasone,

dexamethasone and fluorocortisone; cyclooxygenase II inhibitors such as **rofecoxib**, celecoxib, flosulide, NS-398, DUP-697, **meloxicam**, 6-methoxy-2-naphthylacetic acid, nabumetone, **etodolac**, nimesulide, SC-5766, SC-58215, T-614; salicylates such as salicylic acid, aspirin and diflunisal; pyrazolon derivates such as phenylbutazone and oxyphenbutazone; aminopyridines. . .

DETD . . . C would include an amount of vitamin C sufficient to provide 10% or more of the RDA. Typically, where the **tablet** includes a mineral or vitamin, it will incorporate higher amounts, preferably about 100% or more of the applicable RDA.

DETD [0127] For **oral**, buccal, and sublingual administration, the delivery device may be in the form of a caplet or **tablet**. For rectal administration, the osmotic device can be included in a suppository or **tablet** for release of a therapeutic compound into the intestines, sigmoid flexure and/or rectum. For cutaneous, subcutaneous, otic, intraperitoneal, ophthalmic and implant applications, the device is a solid dosage form adapted for such application and is preferably a **tablet**.

DETD . . . A first layer comprising the active agent was prepared as follows 20.75 g of cisapride monohydrate, 28.15 g of microcrystalline **cellulose**, 37.50 g. of sodium chloride, 45.00 g of poly(ethylene oxide) (200,000 molecular weight), 0.37 g of colloidal silicon dioxide and. . .

DETD . . . wall for covering the uncoated cores was prepared as follows. A polymeric suspension was prepared by dissolving 27.36 g of **cellulose** acetate (average molecular weight 40,000, acetyl content 32% by weight CA), 6.84 g of ammonium methacrylate copolymer (Eudragit.TM. RS 100,. . .

DETD . . . A first layer comprising the active agent was prepared as follows. 16.50 g of micronized nifedipine, 15.00 g of microcrystalline **cellulose**, 32.05 g of sodium chloride, 37.50 g of poly(ethylene oxide) (200,000 molecular weight), 0.75 g of colloidal silicon dioxide and. . .

DETD . . . A wall surrounding the uncoated core was prepared as follows. A polymer suspension was prepared by dissolving 13.3 mg of **cellulose** acetate (average molecular weight 40,000, acetyl content 32% by weight CA), 13.3 mg of **cellulose** acetate (average molecular weight 38,000, acetyl content 39.8% by weight CA), 6.65 g of ammonium methacrylate copolymer (Eudragit.TM. RS 100,. . .

DETD . . . A first layer containing the active agent was prepared as follows. 42.43 g of venlafaxine hydrochloride, 25.22 g of microcrystalline **cellulose**, 37.5 g of sodium chloride, 45 g of poly(ethylene oxide) (200,000 molecular weight), 0.35 g of colloidal silicon dioxide and. . .

DETD . . . wall for covering the uncoated cores was prepared as follows. A polymer suspension was prepared by dissolving 27.36 g of **cellulose** acetate (average molecular weight 40,000, acetyl content 32% by weight CA), 6.84 g of ammonium methacrylate copolymer (Eudragit.TM. RS 100,. . .

DETD Device Having a **Rapid** Release External Coating Containing Drug

DETD . . . delivery system, containing two layers surrounding a central core, including active agent and hydrophilic polymer in the first layer and, **cellulose** acetate and ammonium methacrylate copolymer in the second layer, and having a **rapid** release external coating was manufactured as follows.

DETD . . . The first layer was prepared containing the active agent as follows: 20.75 g of Cisapride monohydrate; 28.15 g of microcrystalline **cellulose**; 37.50 g of sodium chloride; 45.00 g of polyethylene oxide having a 200,000 molecular weight; 0.37 g of colloidal silicon. . .

DETD . . . above tablets which were then coated with a semipermeable wall. A polymer suspension was prepared dissolving 76 weight percent of

cellulose acetate; 19 weight percent of ammonium methacrylate copolymer (Eudragit RS 100, Rohn Pharma) and, 5 weight percent polyethylene glycol 400,. . .

DETD [0148] A **rapid** release external coating was prepared by mixing 33.48 g of ranitidine HCl, 131.02 g of microcrystalline **cellulose**, 25.00 g of povidone, 8.00 g of polyethylene glycol 6000, 1.70 g of polyethylene glycol 400 and 1.00 g of. . . The slugs were milled by passing through a standard USP 20-mesh screen and were blended with 122.30 g of microcrystalline **cellulose**, 0.50 g of colloidal silicon dioxide, 5.00 g of croscarmellose sodium and 2.00 g of magnesium stearate. This final blend. . .

DETD . . . delivery system, containing two layers surrounding a central core, including active agent and hydrophilic polymer in the first layer and, **cellulose** acetate and ammonium methacrylate copolymer in the second layer, and having a delayed release external coating was manufactured as follows:

DETD . . . The first layer was prepared containing the active agent as follows: 20.75 g of cisapride monohydrate; 28.15 g of microcrystalline **cellulose**; 37.50 g of sodium chloride; 45.00 g of polyethylene oxide having a 200,000 molecular weight; 0.37 g of colloidal silicon. . .

DETD . . . above tablets which were then coated with a semipermeable wall. A polymer suspension was prepared dissolving 76 weight percent of **cellulose** acetate; 19 weight percent of ammonium methacrylate copolymer (Eudragit RS 100, Rohn Pharma) and, 5 weight percent polyethylene glycol 400,. . .

DETD [0154] A delayed release external coating was prepared by mixing 33.48 g of ranitidine HCl, 131.02 g of microcrystalline **cellulose**, 25.00 g of povidone, 8.00 g of polyethylene glycol 6000, 1.70 g of polyethylene glycol 400 and 1.00 g of. . . The slugs were milled by passing through a standard USP 20-mesh screen and were blended with 122.30 g of microcrystalline **cellulose**, 0.50 g of colloidal silicon dioxide, 5.00 g of croscarmellose sodium and 2.00 g of magnesium stearate. This final blend. . .

CLM What is claimed is:

. . . micropores for delivery of the at least one active agent by diffusion, and the membrane further comprising one or more **cellulose** esters, one or more poly(methacrylate) copolymer salts and one or more plasticizers, wherein the membrane permits delivery of the at. . .

. . . a drug-containing coat external to the membrane and comprising a second active agent, wherein the drug-containing coat provides an immediate, **rapid**, controlled or delayed release of the second active agent and the external coat surrounds at least a portion of the. . .

. . . A device according to claim 1, wherein the membrane comprises about 1 to 99 weight percent of one or more **cellulose** esters, about 84 to 0.5 weight percent of one or more poly(methacrylate) copolymer salts and about 15 to 0.5 weight. . .

18. A device according to claim 1, wherein the **cellulose** ester is selected form the group consisting of **cellulose** acylate, **cellulose** diacylate, **cellulose** triacylate, **cellulose** acetate, **cellulose** diacetate, **cellulose** triacetate and combinations thereof.

. . . 23. The device of claim 22, wherein the membrane comprises about 1 to 99 weight percent of one or more **cellulose** esters, about 84 to 0.5 weight percent of one or more poly(methacrylate) copolymer salts and about 15 to 0.5 weight. . .

. . . polymer is one or more of hydroxypropyl methylcellulose, alkylcellulose, hydroxyalkylcellulose, poly(alkylene oxide), and combinations thereof; and the at least one **cellulose** ester is

independently selected from the group consisting of **cellulose** acylate, **cellulose** diacylate, **cellulose** triacylate, **cellulose** acetate, **cellulose** diacetate, **cellulose** triacetate and combinations thereof.

27. The device of claim 26, wherein the membrane comprises about 1 to 99 weight percent of one or more **cellulose** esters, about 84 to 0.5 weight percent of one or more poly(methacrylate) copolymer salts and about 15 to 0.5 weight. . .
. . . polymer is one or more of hydroxypropyl methylcellulose, alkylcellulose, hydroxyalkylcellulose, poly(alkylene oxide), and combinations thereof; and the at least one **cellulose** ester is independently selected from the group consisting of **cellulose** acylate, **cellulose** diacylate, **cellulose** triacylate, **cellulose** acetate, **cellulose** diacetate, **cellulose** triacetate and combinations thereof.

30. A device for the controlled delivery of at least one active agent to an environment of use, wherein the. . . with and surrounds the core; and a membrane in contact with and surrounding the layer and comprising one or more **cellulose** esters, one or more poly(methacrylate) copolymer salts and one or more plasticizers, wherein the membrane permits delivery of the at. . .

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SUMM . . . in U.S. Pat. No. 5,474,995 to Ducharme et al., including for example the compound 3-phenyl-4-[4-(methylsulfonyl)phenyl]-5H-furan-2-one, also referred to herein as **rofecoxib**, which has the structure shown in formula (V): ##STR5##

SUMM . . . particularly diclofenac sodium for treating inflammatory diseases of the eye. WO 99/59634 teaches the use of the selective COX-2 inhibitors, **etodolac**, NS-398 and **meloxicam** as anti-inflammatory eye-drops. Recent work suggests that the production of inflammatory amounts of prostaglandins in ocular tissues is the result. . .

SUMM . . . and post-operative inflammation and pain from retinal detachment surgery. Preferred COX-2 inhibitors are celecoxib, deracoxib, valdecoxib, a benzopyran COX-2 inhibitor, **rofecoxib**, etoricoxib, 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one and 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

SUMM . . . In another embodiment, the invention provides a therapeutic method for treating or preventing an ocular COX-2 mediated disorder comprising administering **rofecoxib** to a mammal in need of such treatment, where the disorder is selected from post-operative inflammation and pain from cataract. . .

DETD . . . or substantially simultaneous administration of each therapeutic agent can be effected by any appropriate route including, but not limited to, **oral** routes, intravenous routes, intramuscular routes, and direct absorption through mucous membrane tissues. The therapeutic agents can be administered by the. . .

DETD . . . and post-operative inflammation and pain from retinal detachment surgery. Preferred COX-2 inhibitors are celecoxib, deracoxib, valdecoxib, a benzopyran COX-2 inhibitor, **rofecoxib**, etoricoxib, 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one and 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

DETD . . . In another embodiment, the invention provides a therapeutic method for treating or preventing an ocular COX-2 mediated disorder comprising administering **rofecoxib** to a mammal in need of such treatment, where the disorder is selected from post-operative inflammation and pain from cataract. . .

DETD [0316] **rofecoxib**, 4-[4-(methylsulfonyl)phenyl]-3-phenyl-2 (5H)-furanone; ##STR13##

DETD . . . may be used in the present invention include, but are not limited to celecoxib, deracoxib, valdecoxib, benzopyran COX-2 inhibitors, parecoxib, **rofecoxib**, etoricoxib, 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one and 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

DETD [0398] The **rofecoxib** used in the therapeutic methods of the present invention can be prepared in the manner set forth in U.S. Pat.. . .

DETD . . . solid or a liquid, or both, and is preferably formulated with the compound as a unit-dose composition, for example, a **tablet**, which can contain from 0.05% to 95% by weight of the active compound. Other pharmacologically active substances can also be. . .

DETD [0420] Solid dosage forms for **oral** administration can include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the compounds of this invention are. . . indicated route of administration. If administered per os, a contemplated inhibitor compound can be admixed with lactose, sucrose, starch powder, **cellulose** esters of alkanoic acids, **cellulose** alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia. . . capsules or tablets can contain a controlled-release formulation as can be provided in a dispersion of active compound in hydroxypropylmethyl **cellulose**. In the case of capsules, tablets, and pills, the dosage forms can also comprise buffering agents such as sodium citrate,. . .

DETD [0421] Liquid dosage forms for **oral** administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such. . .

DETD . . . sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for **oral** administration. A contemplated therapeutic compound can be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut. . .

DETD . . . contain ophthalmologically compatible preservatives such as e.g. benzalkonium chloride, surfactants, such as polysorbate 80, liposomes or polymers, for example, methyl **cellulose**, polyvinyl alcohol, polyvinyl pyrrolidone and hyaluronic acid. The latter substances may be used for increasing the viscosity of the solution.. . .

DETD . . . nanoparticles, i.e., solid particles smaller than about 1 pm in their longest dimension. A benefit of this composition is more **rapid** release of the drug, and therefore more complete release during the residence time of the composition in a treated eye,. . .

DETD . . . processes therein described to the preparation of a poorly water soluble selective COX-2 inhibitory drug, for example celecoxib, deracoxib, valdecoxib, **rofecoxib**, 5-chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5-pyridinyl)pyridine and 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one, in nanoparticulate form.

DETD . . . aqueous suspension composition of the invention can comprise a first portion of the drug in nanoparticulate form, to promote relatively **rapid** release, and a second portion of the drug having a D.sub.90 particle size of about 10 .mu.m or greater, that. . .

DETD . . . be affected. Another advantage of the use of selective COX-2 inhibitors is that their reduced systemic side effects make their **oral** use more acceptable, even for the treatment of localized ocular COX-2 mediated conditions. Even in the case where various combinations. . .

DETD . . . cocaine, cromolyn, cyclopentolate, cyproheptadine, demecarium, dexamethasone, dibucaine, diclofenac, diflusinal, dipivefrin, dorzolamide, enoxacin, eperezolid, epinephrine, erythromycin, eserine, estradiol, ethacrynic acid, etidocaine, **etodolac**, fenbufen, fenclofenac, fenclorac, fenoprofen, fentiazac, flufenamic acid, flufenisal, flunoxaprofen, fluorocinolone, fluorometholone, flurbiprofen and esters thereof, fluticasone propionate, furaprofen, furobufen, furofenac,. . .

CLM What is claimed is:

. . . claim 2 wherein the COX-2 inhibitor is selected from the group consisting of celecoxib, deracoxib, valdecoxib, a benzopyran COX-2 inhibitor, **rofecoxib**, etoricoxib, 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one and 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

8. The therapeutic method of claim 3 wherein the COX-2 inhibitor is **rofecoxib**.

28. A therapeutic method for treating or preventing an ocular COX-2 mediated disorder comprising administering an ocular COX-2 mediated disorder-effective amount of **rofecoxib** to a mammal in need of such treatment, wherein the disorder is selected from the group consisting of post-operative inflammation. . .

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DETD [0138] Anti-inflammatory agents having anticoagulant effects on platelets include, for example, non steroidal anti-inflammatory agents such as diclofenac, diflunisal, **etodolac**, fenoprofen, floctafenine, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamate, mefenamic acid, **meloxicam**, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac, tenoxicam, tiaprofenic acid, tolmetin and ketorolac.

DETD [0139] Cyclooxygenase inhibitors include, without limitation, parecoxib, celcoxib, **rofecoxib** and valdecoxib.

DETD . . . part of the composition, or it may be present in a coating on the dosage form, e.g., on a capsule, **tablet**, or caplet, or on each of a plurality of granules, beads, or pellets. In preferred embodiments, the active agent, e.g.,. . .

DETD . . . ergocalciferol, ergotamine, ergotamine tartrate, erythromycin, erythropoietin, essential fatty acids, estramustine, ethacrynic acid, ethambutol, ethinamate, ethinyloestradiol, ethionamide, ethopropazine, ethopropazine HCl, ethotoin, **etodolac**, etoperidone, etoposide, etretinate, famcyclovir, famotidine, felbamate, felodipine, fenbendazole, fenbufen, fenfluramine, fenofibrate, fenolclopam, fenoldopam, fenoprofen, fenoprofen calcium, fentanyl, fexofenadine, finasteride, flecainide,. . .

DETD . . . to whom the pharmaceutical compositions are administered. Such naturally occurring fluids can be the fluids occurring or produced in the **oral** cavity, nasal cavity, respiratory system, digestive system, for example, gastric juice, intestinal fluid, saliva, and lung fluid. The aqueous medium. . .

DETD [0182] Mucoadhesive polymers and polymer-inhibitor conjugates, such as polyacrylate derivatives, chitosan, cellulosics, chitosan-EDTA, chitosan-EDTA-antipain, polyacrylic acid-bacitracin, carboxymethyl **cellulose**-pepstatin, polyacrylic acid-Bwoman-Birk inhibitor.

DETD [0193] Although formulations specifically suited to **oral** administration are presently preferred, the compositions of the present invention can also be formulated for topical, transdermal, buccal, ocular, pulmonary, vaginal, rectal, transmucosal or parenteral administration, as well as for **oral** administration. Thus, the dosage form can be a solution, suspension, emulsion, cream, ointment,

lotion, suppository, spray, aerosol, paste, gel, drops,. . .

DETD [0216] **Rapid** formation: upon dilution with an aqueous medium, the composition forms a clear dispersion very rapidly; i.e., the clear dispersion appears. . .

DETD . . . less prone to suffer from any lag time between administration and absorption caused by the lipolysis process, enabling a more **rapid** onset of therapeutic action and better bioperformance characteristics. In addition, pharmaceutical compositions of the present invention can make use of. . .

DETD . . . site of the therapeutic agent. For example, chenodeoxycholic acid (CDCA) and ursodeoxycholic acid (UDCA) are known enhancers for promoting the **oral** absorption of macromolecules. CDCA and UDCA, particularly UDCA, is practically insoluble in water having a pH at about 7 and. . . however, are advantageous in that the absorption enhancer remains solubilized in the aqueous environment of the stomach and/or intestines following **oral** administration of the composition.

DETD . . . drug in to the aqueous phase, such as large emulsion droplet surface area, and high interfacial transfer resistance, and enable **rapid** completion of the critical partitioning step.

DETD . . . improved permeability of the therapeutic agent across the absorption barrier, e.g., the mucosal membranes in the nasal cavity, in the **oral** cavity, in the gastrointestinal tract, in the lungs and elsewhere in the body. Improved permeability is a result of improved. . .

DETD . . . 44/14 0.35

	Monomul 90L-12	0.15
	Kollidon 30	0.35
	Fenofibrate	0.15
55	Cremophor RH-40	0.57
	Crovol M-40	0.43
	Corn Oil NF	0.40
	Rofecoxib	0.15
56	Cremophor RH-40	0.57
	Kessco PEG 400 MO	0.43
	Soybean Oil NF	0.40
	Nabumetone	0.30
57	Tween 80	0.70
	Tween 85. . .	

CLM What is claimed is:

. . . pharmaceutical composition of claim 1, wherein the dosage form is selected from the group consisting of a pill, capsule, caplet, **tablet**, granule, bead and powder.

. . . 88, wherein the therapeutic agent is selected from the group consisting of clopidrogel, aspirin, ticlidopine, warfarin, dipyridamole, cilostazol, pentoxifylline, celcoxib, **rofecoxib**, parecoxib, valdecoxib and mixtures thereof.

. . . pharmaceutical composition of claim 88, wherein the dosage form is selected from the group consisting of a pill, capsule, caplet, **tablet**, granule, bead and powder.

. . . The method of claim 164, wherein the dosage form is selected from the group consisting of a pill, capsule, caplet, **tablet**, granule, bead and powder.

. . . The method of claim 164, wherein the dosage form is administered by a route selected from the group consisting of **oral**, parenteral, buccal, topical, transdermal, ocular, pulmonary, vaginal, rectal and transmucosal.

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TI **Rapid**-melt semi-solid compositions, methods of making same and methods of using same

AB A novel **rapid**-melt, semi-solid molded composition, including methods of making the same, and methods of using the same for the delivery of prophylactic. . .

SUMM [0002] The present invention relates to a **rapid**-melt, semi-solid composition for delivery of prophylactic and therapeutic active materials to a mammal, methods of making the same, and methods. . .

SUMM . . . may be produced in a variety of dosage forms, depending upon the desired route of administration of the therapeutic material. **Oral** dosage forms, for example, include such solid compositions as tablets, emulsions, and suspensions. The particular dosage form utilized will depend. . .

SUMM [0005] **Tablet** compositions offer many advantages, including ease of product handling, chemical and physical stability, portability (in particular, allowing ready availability to. . . as disorders of the upper gastrointestinal tract, wherein delivery of an active material dissolved or dispersed in a liquid ensures **rapid** and complete delivery to the afflicted area. In an effort to obtain the therapeutic advantages associated with liquid formulations as well as the broad advantages associated with solids, many chewable **tablet** formulations have been developed.

SUMM . . . to be chewed either to provide proper flavor or to increase the surface area of a particular drug to permit **rapid** activity in the digestive tract or circulatory systems. However, many pharmaceutical ingredients usually have both an unpleasant mouth feel and. . .

SUMM [0007] Khankari et al., U.S. Pat. No. 6,024,981, discloses a rapidly dissolving robust dosage form directed to a hard **tablet** that can be packaged, stored and processed in bulk. The solid **tablet** dissolves in the mouth of a patient with a minimum of grit. The **tablet** contains an active ingredient mixed into a matrix of a non-direct compression filler and a relatively high lubricant content.

SUMM [0008] Amselem, U.S. Pat. No. 5,989,583, discloses a dry solid lipid composition suitable as an **oral** dosage form. The composition contains a lipophilic substance, at least one fat which is a solid at about 25.degree. C.. . .

SUMM . . . Nakamichi et al., U.S. Pat. No. 5,837,285, discloses fast soluble tablets that can be produced by a simple method. The **tablet** base is a sugar alcohol. The mixture of the sugar alcohol and a drug is subjected to compressive shaping prior to drying in the process. The dry solid **tablet** can be produced by modification of conventional tableting technology and possesses physicochemical stability.

SUMM [0012] Chavkin et al., U.S. Pat. No. 5,753,255 discloses a chewable medicinal **tablet**. The **tablet** contains about 30 to about 95% by weight of a capric triglyceride and a medicinally active ingredient up to 60%. . .

SUMM [0013] Geyer et al., U.S. Pat. No. 5,320,848, discloses a non-aqueous chewable composition for **oral** delivery of unpalatable drugs. The drug is intimately dispersed or dissolved in a pharmaceutically-acceptable lipid that is solid at room. . .

SUMM [0014] Lapidus, U.S. Pat. No. 4,937,076, discloses a chewable aspirin and buffering material **tablet** in a single dosage form. The buffering materials are integrally dispersed and bound in a fatty material of chocolate, synthetic. . .

SUMM . . . tablets have a harder outer shell which inhibits penetration of liquid, and a softer interior which quickly liquefies when the **tablet** and shell are broken into pieces and contacted by the liquid. The excipient or base material of the **tablet** is made

from carbohydrates held together with small quantities of a carbohydrate binder such as maltodextrin. The tablets can contain. . .

SUMM [0016] Morris et al., U.S. Pat. No. 4,609,543, discloses a soft homogeneous antacid **tablet**. The **tablet** contains solid antacid particles thoroughly coated with a mixture composed of a fatty material or oil, a surfactant, and a. . .

SUMM . . . No. 4,446,135, discloses chewable calcium carbonate-containing antacid tablets having good mouth feel properties. The good mouth feel properties of the **tablet** are obtained by using calcium carbonate of a particular particle size in combination with certain excipients. The calcium carbonate is. . .

SUMM [0018] Puglia et al., U.S. Pat. No. 4,327,077, discloses a compressed chewable antacid **tablet** which has good flexibility, is breakage resistant and disintegrates immediately upon chewing. The **tablet** is formed of a recrystallized fatty material, such as chocolate, a bulking material and an active ingredient bound up in. . .

SUMM [0019] Puglia et al., U.S. Pat. No. 4,327,076, also discloses a compressed chewable antacid **tablet** which has good flexibility, is breakage resistant and disintegrates immediately upon chewing. The **tablet** is formed of particles of the antacid or other active ingredient which are admixed with particles formed of edible fat or oil absorbed on a fat-absorbing material, such as microcrystalline **cellulose**. Upon chewing, the **tablet** is quickly converted to a smooth creamy non-gritty palatable emulsion.

SUMM . . . less palatable after ingestion of multiple doses. Further, the binders and other materials used in such chewable tablets may prevent **rapid** and effective delivery of active materials to the stomach.

SUMM [0021] There is a need for a **rapid**-melt, semi-solid composition that behaves like a liquid when consumed by a mammal, and yet acts like a solid in many. . .

SUMM [0023] Applicant has unexpectedly developed a novel **rapid** -melt, semi-solid molded composition comprising:

SUMM [0029] Applicant has further developed a novel method of preparing a **rapid**-melt, semi-solid molded composition comprising the steps of:

SUMM [0034] Further, Applicant has unexpected developed a novel **rapid** -melt, semi-solid molded composition comprising:

SUMM [0040] In addition, Applicant has developed a **rapid** melt, semi-solid molded composition comprising:

SUMM [0045] Further, Applicant has developed a method of preparing a **rapid**-melt, semi-solid molded composition comprising the steps of:

SUMM [0049] d) molding said final mixture into said **rapid**-melt, semi-solid molded composition.

SUMM [0065] The **rapid**-melt, semi-solid molded compositions of the present inventive subject matter exhibit good resistence to prolonged exposure to heat and the atmosphere. More particularly, the compositions surprisingly maintain their texture and **rapid** melting properties when exposed to those elements.

DETD [0066] The **rapid**-melt, semi-solid molded compositions of the present inventive subject matter contains at least one binder, a salivating agent, an active material, and a diluent/bulking material. The **rapid**-melt, semi-solid compositions may also contain a slipping agent to aid in the transport of the composition from the mouth of. . .

DETD . . . liquefication of the compositions. A further way for the composition to be liquified is by the patient sucking on the **rapid**-melt, semi-solid compositions of the inventive subject matter.

DETD [0071] The **rapid**-melt, semi-solid technology of the present inventive subject matter has multiple applications which are ideal for

the unique properties of the. . .

DETD [0075] The **rapid**-melt, semi-solid compositions of the present inventive subject matter are preferably anhydrous, that is, they do not contain any water. The. . .

DETD [0076] The **rapid**-melt, semi-solid compositions of the present inventive subject matter contain at least one binder. As used herein, "binder" means at least. . .

DETD [0079] The amount of binder present in the **rapid**-melt, semi-solid molded composition of the present inventive subject matter is from about 0.01% to about 70% by weight of the. . .

DETD [0081] The **rapid**-melt, semi-solid molded composition of the present inventive subject matter also contains a salivating agent. As is used herein, "salivating agent". . .

DETD [0084] The amount of salivating agent present in the **rapid**-melt, semi-solid molded composition of the present inventive subject matter is from about 0.05% to about 15% by weight of the. . .

DETD [0086] The **rapid**-melt, semi-solid molded compositions of the present inventive subject matter further contain a diluent/bulking material. The use of a diluent/bulking material. . . lactose, sucrose, sorbitol, fructose, talc, stearic acid, magnesium stearate, dicalcium phosphate, erythitol, xylitol, mannitol, maltitol, isomalt, dextrose, maltose, lactose, microcrystalline **celluloses** and mixtures thereof.

DETD [0088] The **rapid**-melt, semi-solid compositions of the present inventive subject matter may optionally contain a further slipping agent to aid in the palatability. . .

DETD . . . indicated for migraine treatment may be used in the present invention. For example, sumatriptan succinate may be incorporated into the **rapid**-melt semi-solid compositions of the present invention to effectively deliver sumatriptan succinate to a patient in need thereof. In particular, sumatriptan. . .

DETD . . . indicated for treating depression may be used in the present invention. For example, fluoxetine HCl may be incorporated into the **rapid**-melt semi-solid compositions of the present invention to effectively deliver fluoxetine HCl to a patient in need thereof. In particular, fluoxetine. . .

DETD [0101] In particular, alprazolam may be incorporated into the **rapid**-melt semi-solid compositions of the present invention to effectively deliver alprazolam to a patient in need thereof. In particular, alprazolam can. . .

DETD [0103] In particular, zolpidem may be incorporated into the **rapid**-melt semi-solid compositions of the present invention to effectively deliver zolpidem to a patient in need thereof. In particular, zolpidem can. . .

DETD [0107] In particular, omeprazole may be incorporated into the **rapid**-melt semi-solid compositions of the present invention to effectively deliver omeprazole to a patient in need thereof. In particular, omeprazole can. . .

DETD [0113] In particular, simvastin may be incorporated into the **rapid**-melt semi-solid compositions of the present invention to effectively deliver simvastin to a patient in need thereof. In particular, simvastin can. . .

DETD [0116] In particular, loratadine may be incorporated into the **rapid**-melt semi-solid compositions of the present invention to effectively deliver loratadine to a patient in need thereof. In particular, loratadine can. . .

DETD . . . response modifiers, pyrimidine synthesis inhibitors and hyaluronic acid. Specific examples of osteoarthritis and rheumatoid arthritis therapeutics include celecoxib, diclofenac sodium, **rofecoxib**, nabumetone, diclofenac sodium and misoprostol, oxaprozin, **meloxicam**, piroxicam, **etodolac**, naproxen, hylan G-F 20, leflunomide, tenoxicam, and naproxen sodium.

DETD [0119] In particular, celecoxib may be incorporated into the **rapid**-melt semi-solid compositions of the present invention to effectively deliver celecoxib to a patient in need thereof. In particular, celecoxib can. . .

DETD [0122] In particular, doxazosin mesylate may be incorporated into the **rapid**-melt semi-solid compositions of the present invention to effectively deliver doxazosin mesylate to a patient in need thereof. In particular, doxazosin. . .

DETD [0124] In particular, itraconazole may be incorporated into the **rapid**-melt semi-solid compositions of the present invention to effectively deliver itraconazole to a patient in need thereof. In particular, itraconazole can. . .

DETD [0126] In particular, carbamazepine may be incorporated into the **rapid**-melt semi-solid compositions of the present invention to effectively deliver carbamazepine to a patient in need thereof. In particular, carbamazepine can. . .

DETD [0128] In particular, acyclovir may be incorporated into the **rapid**-melt semi-solid compositions of the present invention to effectively deliver acyclovir to a patient in need thereof. In particular, acyclovir can. . .

DETD [0130] The present inventive subject matter contemplates incorporating loperamide hydrochloride into the **rapid**-melt semi-solid compositions as an effective means of delivering the active to a patient in need thereof. The amount of loperamide. . .

DETD . . . The use of the present inventive subject matter to deliver loperamide hydrochloride to a child is especially effective since the **rapid**-melt, semi-solid compositions of the present inventive subject matter do not require any chewing by the patient. As has been previously. . .

DETD . . . mask the unpalatability of the active materials is also well known. Thus, other materials which can be incorporated into the **rapid**-melt, semi-solid molded composition of the present inventive subject matter include flavors, colors and sweeteners. A distinct feature of the inventive **rapid**-melt, semi-solid compositions is that they exhibit excellent taste characteristics. Importantly, it is possible to incorporate high levels of flavors, sweeteners. . .

DETD [0141] The **rapid**-melt, semi-solid compositions of the present inventive subject matter may also be coated in order to facilitate handling of the compositions.. . .

DETD [0142] The present inventive subject matter also contemplates a method of preparing a **rapid**-melt, semi-solid molded composition. It should be recognized that the composition may be prepared by a variety of methods well-known by. . .

DETD [0145] The **rapid**-melt, semi-solid compositions of the present inventive subject matter produced by the above methods have increased product integrity and stability. The. . .

CLM What is claimed is:

1. A **rapid** melt, semi-solid molded composition comprising: at least one binder in an amount from about 0.01% to about 70% by weight;. . .

20. A method of preparing a **rapid**-melt, semi-solid molded composition comprising the steps of: a) melting at least one binder in an amount from about 0.01% to. . . a diluent/bulking material with said active mixture to form a final mixture; and d) molding said final mixture into said **rapid**-melt, semi-solid molded composition.

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SUMM A tachykinin receptor antagonist may be administered alone or in combination by **oral**, parenteral (e.g., intramuscular, intraperitoneal, intravenous or subcutaneous injection, or implant),

nasal, vaginal, rectal, sublingual, or topical routes of administration and. . .

SUMM . . . present invention are in unit dosage forms such as tablets, pills, capsules, powders, granules, solutions or suspensions, or suppositories, for **oral**, parenteral or rectal administration, by inhalation or insufflation or administration by trans-dermal patches or by buccal cavity absorption wafers.

SUMM . . . can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the **tablet** or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an. . . materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and **cellulose** acetate.

SUMM . . . or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the **oral** or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulised by. . .

SUMM Compositions in the form of tablets, pills, capsules or wafers for **oral** administration are particularly preferred.

SUMM . . . antibiotic; anticholinergic agents, such as atropine, hyoscyamine, flavoxate, propantheline, or oxybutynin; a non-steroidal antiinflammatory, such as acetomeniphen, alprostadil, asprin, diclofenac, **etodolac**, ibuprofen, indomethacin, ketoprofe, ketorolac tromethamine, misoprostol, nabumetone, naproxen, naproxen sodium, oxaprozin, piroxicam, spironolactone, spironolactone with hydrochlorothiazide, or trovafloxacin; a corticosteroid; a selective cyclooxygenase-2 inhibitor, such as celecoxib, parecoxib, **rofecoxib**, valdecoxib, **meloxicam**, flosulide, nimesulide, MK-663, NS 398, DuP 697, SC-58125, SC-58635, or RS 57067; or a topical urinary analgesic, such as phenazopyridine,. . .

SUMM . . . then being followed by a patient, concurrent medication, the intrinsic tachykinin receptor antagonist activity of the compound, the bioavailability upon **oral** administration of the compound and other factors which those skilled in the art will recognize.

SUMM Thus, the present invention provides the use of an NK-1 receptor antagonist in an **oral**, once-a-day medicament for treating or preventing acute or chronic prostatitis, chronic nonbacterial prostatitis, acute bacterial prostatitis, prostatodynia, congestive prostatitis, epididymitis,. . .

SUMM . . . the present invention provides a means for the identification of NK-1 receptor antagonists which would be especially effective in an **oral** once-a-day medicament for treating or preventing acute or chronic prostatitis, chronic nonbacterial prostatitis, acute bacterial prostatitis, prostatodynia, congestive prostatitis, epididymitis,. . .

SUMM Furthermore, the exceptional pharmacology of the class of NK-1 receptor antagonists of use in the present invention results in a **rapid** onset of action.

SUMM . . . of an orally active, long acting NK-1 receptor antagonist (as hereinafter defined) for the manufacture of a medicament adapted for **oral** administration for treating or preventing acute or chronic prostatitis, chronic nonbacterial prostatitis, acute bacterial prostatitis, prostatodynia, congestive prostatitis, epididymitis, post-vasectomy. . .

SUMM . . . chronic nonbacterial prostatitis, prostatodynia, congestive prostatitis, epididymitis, post-vasectomy pain and inflammation and/or urethritis in a patient, which method comprises the **oral** administration to a patient in need of such treatment of an effective amount of an orally active, long acting NK-1. . .

SUMM In a further aspect of the present invention, there is provided an **oral** pharmaceutical composition for treating or preventing acute

or chronic prostatitis, chronic nonbacterial prostatitis, acute bacterial prostatitis, prostatodynia, congestive prostatitis, epididymitis,. . .

DETD

EXAMPLE 2

Tablet formulation containing 50-300 mg of NK-1 antagonist

	Amount mg		
NK-1 antagonist	50.0	100.0	300.0
Microcrystalline **cellulose**	80.0	80.0	80.0
Modified food corn starch	80.0	80.0	80.0
Lactose	189.5	139.5	439.5
Magnesium Stearate	0.5	0.5	0.5

DETD The active ingredient, **cellulose**, lactose and a portion of the corn starch are mixed and granulated with 10% corn starch paste. The resulting granulation. . . granulation is then compressed into tablets containing 50 mg, 100 mg and 300 mg of the NK-1 receptor antagonist per **tablet**.

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NEWS	4	Jul 15	Data from 1960-1976 added to RDISCLOSURE
NEWS	5	Jul 21	Identification of STN records implemented
NEWS	6	Jul 21	Polymer class term count added to REGISTRY
NEWS	7	Jul 22	INPADOC: Basic index (/BI) enhanced; Simultaneous Left and Right Truncation available
NEWS	8	AUG 05	New pricing for EUROPATFULL and PCTFULL effective August 1, 2003
NEWS	9	AUG 13	Field Availability (/FA) field enhanced in BEILSTEIN
NEWS	10	AUG 15	PATDPAFULL: one FREE connect hour, per account, in September 2003
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NEWS	12	AUG 15	RDISCLOSURE: one FREE connect hour, per account, in September 2003
NEWS	13	AUG 15	TEMA: one FREE connect hour, per account, in September 2003
NEWS	14	AUG 18	Data available for download as a PDF in RDISCLOSURE
NEWS	15	AUG 18	Simultaneous left and right truncation added to PASCAL
NEWS	16	AUG 18	FROSTI and KOSMET enhanced with Simultaneous Left and Righ Truncation
NEWS	17	AUG 18	Simultaneous left and right truncation added to ANABSTR
NEWS	18	SEP 22	DIPPR file reloaded

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                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

FILE 'USPATFULL' ENTERED AT 14:53:58 ON 23 SEP 2003
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FILE COVERS 1971 TO PATENT PUBLICATION DATE: 23 Sep 2003 (20030923/PD)
FILE LAST UPDATED: 23 Sep 2003 (20030923/ED)
HIGHEST GRANTED PATENT NUMBER: US6625813
HIGHEST APPLICATION PUBLICATION NUMBER: US2003177560
CA INDEXING IS CURRENT THROUGH 23 Sep 2003 (20030923/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 23 Sep 2003 (20030923/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Aug 2003
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Aug 2003

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>>>  applications.  USPAT2 contains full text of the latest US         <<<
>>>  publications, starting in 2001, for the inventions covered in     <<<
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>>>  publications.  The publication number, patent kind code, and      <<<
>>>  publication date for all the US publications for an invention     <<<
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>>>  /PK, etc.                                                         <<<

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>>>  classifications, or claims, that may potentially change from      <<<
>>>  the earliest to the latest publication.                           <<<

This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> s rofecoxib and mannitol and croscarmellose and silicon dioxide and magnesium
stearate
           427 ROFECOXIB
         44206 MANNITOL
          2445 CROSCARMELLOSE
        357973 SILICON
        252973 DIOXIDE
         68615 SILICON DIOXIDE
                 (SILICON(W)DIOXIDE)
        249780 MAGNESIUM
        102886 STEARATE
         58020 MAGNESIUM STEARATE
                 (MAGNESIUM(W)STEARATE)
L1          10 ROFECOXIB AND MANNITOL AND CROSCARMELLOSE AND SILICON DIOXIDE
               AND MAGNESIUM STEARATE

=> d l1 1-10

L1   ANSWER 1 OF 10  USPATFULL on STN
AN     2003:231677  USPATFULL
TI     Fast dissolving tablets of cyclooxygenase-2 enzyme inhibitors
IN     Murpani, Deepak, New Delhi, INDIA
```

Arora, Vinod Kumar, New Delhi, INDIA
Malik, Rajiv, New Delhi, INDIA
PI US 2003161875 A1 20030828
AI US 2002-85664 A1 20020227 (10)
DT Utility
FS APPLICATION
LN.CNT 373
INCL INCLM: 424/465.000
INCLS: 514/406.000
NCL NCLM: 424/465.000
NCLS: 514/406.000
IC [7]
ICM: A61K031-415
ICS: A61K009-20
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 2 OF 10 USPATFULL on STN
AN 2003:206914 USPATFULL
TI Drug mixture with enhanced dissolution rate
IN Ewing, Gary D., Kalamazoo, MI, UNITED STATES
Hawley, Michael, Kalamazoo, MI, UNITED STATES
Coffey, Martin J., Portage, MI, UNITED STATES
Price, Jeffrey E., Middlebury, IN, UNITED STATES
MacMillan, Stephen P., Newton, PA, UNITED STATES
PI US 2003143271 A1 20030731
AI US 2003-337583 A1 20030107 (10)
PRAI US 2002-346560P 20020107 (60)
DT Utility
FS APPLICATION
LN.CNT 1076
INCL INCLM: 424/468.000
INCLS: 424/452.000; 514/161.000
NCL NCLM: 424/468.000
NCLS: 424/452.000; 514/161.000
IC [7]
ICM: A61K009-48
ICS: A61K009-22
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 3 OF 10 USPATFULL on STN
AN 2003:120747 USPATFULL
TI Blood cell deficiency treatment method
IN Ahlem, Clarence N., San Diego, CA, UNITED STATES
Reading, Christopher, San Diego, CA, UNITED STATES
Frincke, James, San Diego, CA, UNITED STATES
Stickney, Dwight, Granite Bay, CA, UNITED STATES
Lardy, Henry A., Madison, WI, UNITED STATES
Marwah, Padma, Middleton, WI, UNITED STATES
Marwah, Ashok, Middleton, WI, UNITED STATES
Prendergast, Patrick T., Straffan, IRELAND
PI US 2003083231 A1 20030501
AI US 2002-87929 A1 20020301 (10)
RLI Continuation-in-part of Ser. No. US 2000-675470, filed on 28 Sep 2000, PENDING Continuation-in-part of Ser. No. US 2001-820483, filed on 29 Mar 2001, PENDING Continuation-in-part of Ser. No. US 2000-535675, filed on 23 Mar 2000, PENDING Continuation-in-part of Ser. No. US 1999-449004, filed on 24 Nov 1999, ABANDONED Continuation-in-part of Ser. No. US 1999-449184, filed on 24 Nov 1999, ABANDONED Continuation-in-part of Ser. No. US 1999-449042, filed on 24 Nov 1999, ABANDONED Continuation-in-part of Ser. No. US 1999-461026, filed on 15 Dec 1999, ABANDONED Continuation-in-part of Ser. No. US 2000-586673, filed on 1 Jun 2000, ABANDONED Continuation-in-part of Ser. No. US 2000-586672,

filed on 1 Jun 2000, ABANDONED Continuation-in-part of Ser. No. US 1999-414905, filed on 8 Oct 1999, ABANDONED
PRAI US 1999-161453P 19991025 (60)
US 2001-272624P 20010301 (60)
US 2001-323016P 20010911 (60)
US 2001-340045P 20011130 (60)
US 2001-328738P 20011011 (60)
US 2001-338015P 20011108 (60)
US 2001-343523P 20011220 (60)
US 1999-126056P 19991019 (60)
US 1999-124087P 19990311 (60)
US 1998-109923P 19981124 (60)
US 1998-109924P 19981124 (60)
US 1998-110127P 19981127 (60)
US 1998-112206P 19981215 (60)
US 1999-145823P 19990727 (60)
US 1999-137745P 19990603 (60)
US 1999-140028P 19990616 (60)
DT Utility
FS APPLICATION
LN.CNT 19428
INCL INCLM: 514/002.000
INCLS: 514/063.000; 514/026.000; 514/044.000; 514/169.000; 514/173.000
NCL NCLM: 514/002.000
NCLS: 514/063.000; 514/026.000; 514/044.000; 514/169.000; 514/173.000
IC [7]
ICM: A61K038-16
ICS: A61K048-00; A61K031-704; A61K031-695; A61K031-56; A61K031-58
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 4 OF 10 USPATFULL on STN
AN 2003:113559 USPATFULL
TI Fused bicyclic or tricyclic amino acids
IN Blakemore, David Clive, Sandwich, UNITED KINGDOM
Bryans, Justin Stephen, Sandwich, UNITED KINGDOM
Williams, Sophie Caroline, Sandwich, UNITED KINGDOM
PA Pfizer Inc. (non-U.S. corporation)
PI US 2003078300 A1 20030424
US 6596900 B2 20030722
AI US 2002-124210 A1 20020416 (10)
PRAI GB 2001-9635 20010419
GB 2001-25897 20011026
DT Utility
FS APPLICATION
LN.CNT 2247
INCL INCLM: 514/561.000
INCLS: 562/501.000; 562/442.000
NCL NCLM: 562/501.000
IC [7]
ICM: A61K031-195
ICS: C07C229-28; C07C229-34
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 5 OF 10 USPATFULL on STN
AN 2002:242824 USPATFULL
TI Combined diffusion / osmotic pumping drug delivery system
IN Faour, Joaquina, Buenos Aires, ARGENTINA
PI US 2002132005 A1 20020919
AI US 2002-47915 A1 20020115 (10)
RLI Continuation-in-part of Ser. No. US 2000-483282, filed on 14 Jan 2000, GRANTED, Pat. No. US 6352721
PRAI WO 2001-US562 20010108

DT Utility
FS APPLICATION
LN.CNT 1705
INCL INCLM: 424/473.000
NCL NCLM: 424/473.000
IC [7]
ICM: A61K009-24
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 6 OF 10 USPATFULL on STN
AN 2002:221058 USPATFULL
TI Oral fast-melt formulation of a cyclooxygenase-2 inhibitor
IN Le, Trang T., Mundelein, IL, UNITED STATES
Kararli, Tugrul T., Skokie, IL, UNITED STATES
Kontny, Mark J., Libertyville, IL, UNITED STATES
Sastry, Srikonda V., Sunnyvale, CA, UNITED STATES
Nyshadham, Janaki R., Fremont, CA, UNITED STATES
Pagliero, Arthur J., JR., Vacaville, CA, UNITED STATES
PI US 2002119193 A1 20020829
AI US 2001-932494 A1 20010817 (9)
PRAI US 2000-226349P 20000818 (60)
DT Utility
FS APPLICATION
LN.CNT 1634
INCL INCLM: 424/465.000
INCLS: 514/406.000; 514/378.000; 514/277.000; 514/473.000
NCL NCLM: 424/465.000
NCLS: 514/406.000; 514/378.000; 514/277.000; 514/473.000
IC [7]
ICM: A61K009-20
ICS: A61K031-435
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 7 OF 10 USPATFULL on STN
AN 2002:149172 USPATFULL
TI Selective cyclooxygenase-2 inhibitors and vasomodulator compounds for generalized pain and headache pain
IN Hassan, Fred, Peapack, NJ, UNITED STATES
Forbes, James C., Skokie, IL, UNITED STATES
PI US 2002077328 A1 20020620
AI US 2001-905292 A1 20010713 (9)
PRAI US 2001-296196P 20010606 (60)
US 2001-284248P 20010417 (60)
US 2000-218101P 20000713 (60)
DT Utility
FS APPLICATION
LN.CNT 4527
INCL INCLM: 514/263.310
INCLS: 514/263.320
NCL NCLM: 514/263.310
NCLS: 514/263.320
IC [7]
ICM: A61K031-522
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 8 OF 10 USPATFULL on STN
AN 2002:140876 USPATFULL
TI Rapidly disintegrating oral formulation of a cyclooxygenase-2 inhibitor
IN Kararli, Tugrul T., Skokie, IL, UNITED STATES
Kontny, Mark J., Libertyville, IL, UNITED STATES
Le, Trang T., Mundelein, IL, UNITED STATES
PI US 2002071857 A1 20020613

AI US 2001-932537 A1 20010817 (9)
PRAI US 2000-226487P 20000818 (60)
DT Utility
FS APPLICATION
LN.CNT 1452
INCL INCLM: 424/435.000
INCLS: 514/406.000; 514/456.000; 514/690.000
NCL NCLM: 424/435.000
NCLS: 514/406.000; 514/456.000; 514/690.000
IC [7]
ICM: A61K031-415
ICS: A61K031-353; A61K031-12
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 9 OF 10 USPATFULL on STN
AN 2002:92708 USPATFULL
TI Oral fast-melt dosage form of a cyclooxygenase-2 inhibitor
IN Kararli, Tugrul T., Skokie, IL, UNITED STATES
Kontny, Mark J., Libertyville, IL, UNITED STATES
Le, Trang T., Mundelein, IL, UNITED STATES
PI US 2002049233 A1 20020425
AI US 2001-932500 A1 20010817 (9)
PRAI US 2000-226347P 20000818 (60)
DT Utility
FS APPLICATION
LN.CNT 1131
INCL INCLM: 514/332.000
INCLS: 514/340.000; 514/341.000; 514/407.000; 514/379.000; 514/471.000; 514/602.000; 264/109.000
NCL NCLM: 514/332.000
NCLS: 514/340.000; 514/341.000; 514/407.000; 514/379.000; 514/471.000; 514/602.000; 264/109.000
IC [7]
ICM: A61K031-4439
ICS: A61K031-42; A61K031-415; A61K031-18; A61K031-34; B27N003-00
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 10 OF 10 USPATFULL on STN
AN 2002:12569 USPATFULL
TI Solid-state form of celecoxib having enhanced bioavailability
IN Hageman, Michael J., Portage, MI, UNITED STATES
He, Xiaorong, Kalamazoo, MI, UNITED STATES
Kararli, Tugrul T., Skokie, IL, UNITED STATES
Mackin, Lesley A., Evanston, IL, UNITED STATES
Miyake, Patricia J., Tower Lakes, IL, UNITED STATES
Rohrs, Brian R., Scotts, MI, UNITED STATES
Stefanski, Kevin J., Kalamazoo, MI, UNITED STATES
PI US 2002006951 A1 20020117
AI US 2000-730663 A1 20001206 (9)
PRAI US 1999-169856P 19991209 (60)
DT Utility
FS APPLICATION
LN.CNT 1354
INCL INCLM: 514/406.000
INCLS: 548/377.100
NCL NCLM: 514/406.000
NCLS: 548/377.100
IC [7]
ICM: A61K031-415
ICS: C07D231-12
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d l1 1-10 kwic

L1 ANSWER 1 OF 10 USPATFULL on STN

SUMM . . . COX-2 enzyme inhibitors that are advantageously administered by the pharmaceutical compositions of this invention include "specific inhibitors" such as celecoxib, **rofecoxib**, parecoxib, valdecoxib, and the like or "preferential inhibitors" such as meloxicam, nimesulide, etodolac, nabumetone, and the like.

SUMM . . . sulfate, calcium carbonate, calcium hydroxide, aluminium hydroxide, magnesium silicate, aluminium magnesium hydroxide; carbohydrates such as directly compressible maltose, maltitol, sorbitol, **mannitol**, glucose, sucrose, xylitol, lactose, lactose monohydrate, erythritol, fructose, maltodextrins; celluloses such as microcrystalline cellulose, calcium carboxy methyl cellulose; starches such. . .

SUMM . . . about 80 weight percent of the COX-2 inhibitor compositions of this invention. One of the preferred fillers is directly compressible **mannitol**.

SUMM . . . not only is free-flowing but also sufficiently cohesive to act as a binder. Materials such as microcrystalline cellulose, microcrystalline dextrose, **mannitol**, directly compressible dicalcium phosphate, amylose and polyvinylpyrrolidone have such properties.

SUMM . . . as microcrystalline cellulose, hydroxypropyl cellulose or carboxymethyl cellulose; algins such as sodium alginate or alginic acid; cross-linked cellulose such as **croscarmellose** sodium; gums such as guar gum or xanthan gum; cross-linked polymers such as crospovidone; effervescent agent such as sodium bicarbonate. . .

SUMM . . . percent and most preferably about 2.0 weight percent of the COX-2 inhibitor compositions by this invention. The preferred disintegrant is **croscarmellose** sodium.

SUMM [0031] The lubricants of the present invention may be selected from talc, **magnesium stearate**, calcium stearate, stearic acid, magnesium lauryl sulphate and hydrogenated vegetable oil. Soluble lubricants include sodium benzoate, a mixture of sodium. . .

SUMM . . . weight percent, and most preferably 1.0 weight percent of the COX-2 inhibitor compositions of this invention. The preferred lubricant is **magnesium stearate**.

SUMM [0033] The glidants of the present invention may be selected from colloidal **silicon dioxide** and talc.

SUMM . . . mannose, galactose, fructose, dextrose, sucrose, maltose, partially hydrolyzed starch, or corn syrup solids and sugar alcohols such as sorbitol, xylitol, **mannitol** and mixtures thereof; water-soluble artificial sweeteners such as the soluble saccharin salts, cyclamate salts, acesulfam-K and the like, and free. . .

DETD [0040]

Rofecoxib mouth dissolving tablets-25 mg.

Ingredient	Quantity (mg)
Rofecoxib	25.28
Aspartame	0.35
Mannitol	166.67
Croscarmellose sodium	4.00
Colloidal **silicon dioxide**	1.00
Mixed fruit flavour	0.70
Magnesium stearate	2.00
Total	200.00

DETD [0041] 1. **Rofecoxib**, aspartame, **mannitol**, **croscarmellose** sodium, colloidal **silicon**

dioxide and mixed fruit flavour are sifted through the sieve #44 BSS and admixed for about 15 minutes to make a. . .

DETD [0042] 2. **Magnesium stearate** is passed through sieve #100 BSS and mixed with the blend of step 1 for sufficient time.

DETD . . . seconds, whereas the mouth dissolving time was less than 25 seconds. The friability was about 0.4% w/w. The mouth dissolving **rofecoxib** tablets are tested in 1% sodium lauryl sulphate (SLS) according to the procedure described in the United States Pharmacopoeia XXIII, Apparatus 1 @ 100 rpm and found to have the following release profile:

Time (Minutes)	% **Rofecoxib** dissolved
15	74
30	83
45	88

DETD [0045]

Ingredient	Quantity (mg)
Rofecoxib	50.56
Aspartame	0.70
Mannitol	333.34
Croscarmellose sodium	8.0
Colloidal **silicon dioxide**	2.0
Mixed fruit flavour	1.4
Magnesium stearate	4.0
Total	400.0

DETD [0047] The **rofecoxib** mouth dissolving tablet of 50 mg strength had an average weight of 400.+-.20 mg, thickness of 4.9.+-.0.2 mm, hardness of. . .

DETD [0048]

Nimesulide mouth dissolving tablet-100 mg.

Ingredient	Quantity (mg)
Nimesulide	100.00
Aspartame	4.5
Mannitol	318.75
Croscarmellose sodium	10.5
Colloidal **silicon dioxide**	2.25
Orange flavour	4.5
Monosodium citrate	5.0
Magnesium stearate	4.5
Total	450.0

CLM What is claimed is:

5. The tablet according to claim 4 wherein the COX-2 inhibitor is selected from the group consisting of meloxicam, **rofecoxib**, celecoxib, valdecoxib, parecoxib, nabumetone, nimesulide and etodolac.

. . . phosphate dihydrate, tricalcium phosphate, calcium sulfate, calcium carbonate, calcium hydroxide, aluminium hydroxide, magnesium silicate, aluminium magnesium hydroxide, maltose, maltitol, sorbitol, **mannitol**, glucose, sucrose, xylitol, lactose, lactose monohydrate, erythritol, fructose, maltodextrins, microcrystalline cellulose, calcium carboxy methyl cellulose, pregelatinized starch, potato starch, maize. . .

. . . 9. The tablet according to claim 8 wherein the binders may be

selected from the group consisting of microcrystalline cellulose, **mannitol**, microcrystalline dextrose, directly compressible dicalcium phosphate, amylose and polyvinylpyrrolidone.

. . . glycolate, corn starch, potato starch, pregelatinized starch, bentonite, montmorillonite, veegum, microcrystalline cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, alginic acid, **croscarmellose** sodium, guar gum, xanthan gum, crospovidone; sodium bicarbonate and citric acid, and mixtures thereof.

12. The tablet according to claim 8 wherein the lubricants may be selected from the group consisting of talc, **magnesium stearate**, calcium stearate, stearic acid, magnesium lauryl sulphate and hydrogenated vegetable oil, sodium benzoate, sodium acetate, sodium chloride, leucine, sodium stearyl. . .
13. The tablet according to claim 8 wherein the glidants may be selected from the group consisting of colloidal **silicon dioxide** and talc.

. . . sweetener may be selected from the group consisting of xylose, ribose, glucose, mannose, galactose, fructose, dextrose, sucrose, maltose, sorbitol, xylitol, **mannitol**, soluble saccharin salts, cyclamate salts, acesulfam-K and free acid form of saccharin and dipeptide based sweeteners, and mixtures thereof.

20. A mouth dissolving tablet of COX-2 inhibitor consisting of a COX-2 inhibitor, **croscarmellose** sodium, **mannitol**, aspartame, colloidal **silicon dioxide**, **magnesium stearate** and flavouring agent.

L1 ANSWER 2 OF 10 USPATFULL on STN

SUMM . . . other useful therapeutic effects while minimizing or eliminating such adverse side effects. Selective COX-2 inhibitory drugs such as celecoxib and **rofecoxib**, first commercially available in 1999, have therefore represented a major advance in the art. These drugs are formulated in a. . .

SUMM [0007] Greenberg et al. (2000), J. Clin. Pharmacol. 40(12), 1509-1515, reported that the selective COX-2 inhibitor **rofecoxib** administered in combination with low-dose aspirin did not alter antiplatelet effects of the aspirin in healthy subjects. However, Boers (2001),. . .

SUMM . . . platelet cyclooxygenase-1 inactivation by aspirin," Proc. Nat. Acad. Sci. 98(25), 14583-14588, found that the selective COX-2 inhibitors celecoxib, valdecoxib and **rofecoxib** had some antagonistic effect on the antiplatelet activity of aspirin, but it was not clear whether the effect was clinically. . .

DETD [0041] Illustratively, celecoxib, deracoxib, valdecoxib, **rofecoxib**, etoricoxib, 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one, (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3-(2H)-pyridazinone, 5-methyl-2-(2'-chloro-6'-fluoroanilino)phenylacetic acid and their salts, more particularly celecoxib, valdecoxib, **rofecoxib** and etoricoxib, are useful in a composition of the invention.

DETD . . . combination, lactose, including anhydrous lactose and lactose monohydrate; starches, including directly compressible starch and hydrolyzed starches (e.g., Celutab.TM. and Emdex.TM.); **mannitol**; sorbitol; xylitol; dextrose (e.g., Cerelose.TM. 2000) and dextrose monohydrate; dibasic calcium phosphate dihydrate; sucrose-based diluents; confectioner's sugar; monobasic calcium sulfate. . .

DETD . . . 1550, and Colorcon.TM. 1500), clays (e.g., Veegum.TM. HV), celluloses such as purified cellulose, microcrystalline cellulose, methylcellulose, carmellose and carmellose sodium, **croscarmellose** sodium (e.g., Ac-Di-Sol.TM. of FMC), alginates, crospovidone, and gums such as agar, guar, locust bean, karaya, pectin and tragacanth gums.

DETD [0051] **Croscarmellose** sodium is a preferred disintegrant, and, if present, preferably constitutes about 0.2% to about 10%, more preferably about 0.2% to about 7%, and still more preferably about 0.2% to about 5%, of the total weight of the composition. **Croscarmellose** sodium confers superior intragranular disintegration properties to granulated compositions.

DETD [0057] **Magnesium stearate** is a preferred lubricant used, for example, to reduce friction between tableting equipment and a granulated mixture during compression of. . .

DETD [0059] Glidants can be used to promote powder flow of a solid formulation. Suitable glidants include colloidal **silicon dioxide**, starch, talc, tribasic calcium phosphate, powdered cellulose and magnesium trisilicate. Colloidal **silicon dioxide** is particularly preferred.

CLM What is claimed is:

. . . 5. The composition of claim 1 wherein said coxib component is selected from the group consisting of celecoxib, deracoxib, valdecoxib, **rofecoxib**, etoricoxib, 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one, (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)-phenyl]-3-(2H)-pyridazinone, 5-methyl-2-(2'-chloro-6'-fluoroanilino)phenyl-acetic acid and salts thereof.

6. The composition of claim 1 wherein said coxib component is selected from the group consisting of celecoxib, valdecoxib, **rofecoxib** and etoricoxib.

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SUMM . . . microcrystalline cellulose, gum arabic, polysorbate 80, butylparaben, propylparaben, methylparaben, BHA, EDTA, sodium lauryl sulfate, sodium chloride, potassium chloride, titanium dioxide, **magnesium stearate**, castor oil, olive oil, vegetable oil, buffering agents such as sodium hydroxide, monobasic sodium phosphate, dibasic sodium phosphate, potassium hydroxide,. . . monobasic potassium phosphate, dibasic potassium phosphate, tribasic potassium phosphate, potassium carbonate, potassium bicarbonate, ammonium hydroxide, ammouium chloride, saccharides such as **mannitol**, glucose, fructose, sucrose or lactose any of which may be compressible or any of which may be spray dried.

SUMM . . . or unit dosage forms that contain the hemihydrate. Exemplary excipients include or or more of those disclosed herein, e.g., sucrose, **mannitol**, starch, carboxymethyl cellulose, **magnesium stearate** and the like.

SUMM . . . such as BrEA hemihydrate comprising per 25 mg of the formula 1 compound about 6.2 mg povidone, about 0.62 mg **magnesium stearate**, about 45 mg **mannitol** and about 48 mg of compressible sucrose.

SUMM . . . a polyhydric alcohol, i.e. an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, butane 1,4-diol, **mannitol**, sorbitol, glycerol and a polyethylene glycol (including, e.g., PEG 300 and PEG 400) and mixtures thereof. The topical formulations may. . .

SUMM . . . benzyl benzoate; (3) about 1-60 mg/mL of a formula 1 compound(s), about 25% PEG300, about 35% propylene glycol, about 35%

mannitol and about 5% benzyl benzoate; (4) about 1-60 mg/mL of a formula 1 compound(s), about 57.5% propylene glycol, a mixture. . . PEG200 (e.g., PEG300:PEG200 in a ratio a 20 of about 1:10 to about 10:1), about 35% propylene glycol, about 35% **mannitol** and about 5% benzyl benzoate; (7) any of formulations (1) through (6) where the formula 1 compound(s) is about 40-55. . .

SUMM . . . one, two, three or more excipients such as fillers, binders, lubricants, antioxidants, preservatives, flavoring agents or disintegrants, e.g., lactose, sucrose, **mannitol**, Tween-80, **magnesium stearate**, butylated hydroxyanisole, butylated hydroxytoluene, cyclodextrins (e.g., .alpha.-cyclodextrins, .beta.-cyclodextrins, .gamma.-cyclodextrins, hydroxypropyl-.beta.-cyclodextrin), carbomers, hydrolyzed polyvinylalcohol, polyethylene oxide, polyacrylates, hydroxypropylmethylcellulose, hydroxypropylcellulose, and combinations. . .

SUMM . . . about 0.01 wt. % to 0.5 wt. %, of the dosage unit. Suitable lubricants include, but are not limited to, **magnesium stearate**, calcium stearate, stearic acid, sodium stearylfumarate, talc, hydrogenated vegetable oils and polyethylene glycol. However, modulating the particle size of the. . .

SUMM . . . dextrin (e.g., co-crystallized sucrose and dextrin such as Di-Pak.TM., which may be obtained from Amstar), lactone, calcium phosphate, cellulose, kaolin, **mannitol**, sodium chloride, dry starch, powdered sugar and the like. Binders, if used, are those that enhance adhesion. Examples of such. . .

SUMM . . . Flavorings are optionally included in buccal or sublingual formulations. Any suitable flavoring may be used, e.g., one or more of **mannitol**, sucrose, glucose, lactose, lemon, lemon lime, orange, menthol or artificial sweeteners such as aspartame, saccharin sodium, dipotassium glycyrrhizinate, stevia and. . .

SUMM . . . cellulose and (iv) a disintegrant, e.g., crospovidone. These formulations are capable of buccal disintegration or dissolution and may further comprise **mannitol**. These formulations may dissolve completely in solely saliva within about 1-10 minutes of administration to a subject. The erythritol is. . . crystalline cellulose and (iv) about 3-7 parts by weight of a disintegrant, which optionally is one or more of crospovidone, **croscarmellose**, **croscarmellose** sodium, carmellose calcium, carboxymethylstarch sodium, low substituted hydroxypropyl cellulose or corn starch. Examples of the crystalline cellulose include products of. . .

SUMM . . . swellable hydrophilic excipient, a water-soluble or a water-dispersible excipient, e.g., one or more of partially hydrolyzed gelatin, hydrolyzed dextran, dextrin, **mannitol**, alginates, polyvinyl alcohol, polyvinyl pyrrolidine, water soluble cellulose derivatives, methylcellulose, ethyl cellulose, carboxymethyl cellulose, hydroxymethylcellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, alginates,. . .

SUMM . . . the C.sub.H2 and C.sub.H3 domain and hinge regions of IgG1) or a COX-2 inhibitor such as celexicob (4-5[-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl] benzenesulfonamide) or **rofecoxib** (4-[4-methylsulfonyl)phenyl]-3-phenyl-2 (5H)-furanone), antimalarial agents, antimicrobials, antimigraine agents, antimycotic agents, antinausea agents, antineoplastic agents, antiparasitics, antiparkinsonian agents, antiproliferatives, antiprostatic hypertrophy agents,. . .

SUMM . . . the C.sub.H2 and C.sub.H3 domain and hinge regions of IgG1) or a COX-2 inhibitor such as celexicob (4-5[-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl] benzenesulfonamide) or **rofecoxib** (4-[4-methylsulfonyl)phenyl]-3-phenyl-2 (5H)-furanone) or an IL-1 receptor antagonist such as anakinra), cardiac drugs (e.g., digitoxin), .beta.-blockers or antihypertensive drugs (e.g., oxprenolol. . .

SUMM . . . with an effective amount of a composition comprising a formula 1 compound, erythritol, a crystalline cellulose, a crospovidone and optionally **mannitol**. The composition may comprise a formulation that comprises about 0.1 to about 100 mg, e.g., about 10, 20, 25, 30. . .

SUMM . . . The method of embodiments 17F-20F wherein the formula 1 compound, the erythritol, the crystalline cellulose, the crospovidone and the optional **mannitol**, are uniformly mixed.

DETD . . . (RBC). Washed RBC are infected with schizonttrophozoite parasite stages (Palo Alto strain, mycoplasma-free). Stage specific parasites are isolated by the Percoll-**mannitol** method. Briefly, normal schizont-stage parasitized RBC (SPE) separated on Percoll-**mannitol** gradient (parasitemia >95% SPE) are mixed with RBC suspended in growth medium (RPMI 1640 medium containing 25 mmol/L Hepes, 20. . . at 40-44 hours after inoculum parasites are at schizont-stage in the first cycle. RPE, TPE and SPE are separated on Percoll-**mannitol** gradients. The parasitemia is usually 8-10% RPE, and >95% TPE. Nonparasitized and parasitized RBC are counted electronically. To assess total. . .

DETD . . . was prepared using compressible sucrose. The caplets each contained 25 mg BrEA hemihydrate, 6.25 mg povidone (1-ethenyl-2-pyrrolidinone polymer), 0.62 mg **magnesium stearate**, 45 mg **mannitol** and 48.12 mg of compressible sucrose. Sterile BrEA and excipients were used to prepare the caplets. The formulation is suitable. . .

DETD . . . kg BrEA, 3.25 Kg Fast Flo Lactose (Foremost), 0.250 kg Polyplasdone XL .sub.10TM (crospovidone NF), 0.100 kg Syloid 244FP (colloidal **silicon dioxide**), 0.250 Kg **mannitol** (USP) 0.050 kg Cab-O-Sil.TM. (amorphous silica) and 0.100 Kg magnseium stearate. Tablets contining 25 mg each of BrEA were prepared. . .

DETD . . . delivery, e.g., buccal or sublingual administration, was prepared that comprised per tablet 20% w/w BrEA, 55% w/w lactose, 15% w/w **mannitol**, 5% w/w crospovidone, 2% w/w **magnesium stearate**, 3% w/w silica.

DETD . . . process. Blending was continued, if needed, until the blend contained 19% to 21% of 16.alpha.-fluoroandrost-5-ene-17-one by weight in selected samples. **Magnesium stearate**, sieved through a #40 screen, was then added to the mixture and blended for 5 minutes.

DETD [1586] Excipients used in the formulation were **mannitol**, (Pearlitol.TM., 200 .mu.m diameter granules, Roquette), which provided a matrix for separation of drug particles in the tablet and a. . . CA), NF, was used as a wetting and dispersion agent. Sodium lauryl sulfate, NF, was used as a dispersion agent. **Magnesium stearate** (Spectrum Quality Products, Gardena, Calif.), NF, was used as a lubricant to facilitate ejection of tablets from the die. Amorphous. . . in weight. The final composition of the tablets is shown below.

Component	% w/w	mg/tablet	Total weight (g)
16.alpha.-fluoroandrost-5-ene-17-one	16	20	700
Mannitol	72	90	3150
Crospovidone	7	8.75	306.2
Magnesium stearate	2	2.5	87.5
PEG 3350	1	1.25	43.8
Sodium lauryl sulfate	1	1.25	43.8
Cab-O-Sil .TM.	1	1.25	43.8
Total	100%	125 mg	4375.1

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SUMM [0089] (xviii) COX-2 inhibitors, e.g. celecoxib, **rofecoxib** and valdecoxib;

SUMM . . . as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate, glycine and starch (preferably corn, potato or tapioca starch), **mannitol**, disintegrants such as sodium starch glycolate, crosscarmellose sodium and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC),. . . triglycerides, hydroxypropylcellulose (HPC), bentonite sucrose, sorbitol, gelatin and acacia. Additionally, lubricating agents may be added to solid compositions such as **magnesium stearate**, stearic acid, glyceryl behenate, PEG and talc or wetting agents, such as sodium lauryl sulphate. Additionally, polymers such as carbohydrates,. . .

SUMM [0103] Fast dispersing or dissolving dosage fromulations (FDDFs) may contain the following ingredients: aspartame, acesulfame potassium, citric acid, **croscarmellose** sodium, crospovidone, diascorbic acid, ethyl acrylate, ethyl cellulose, gelatin, hydroxypropylmethyl cellulose, **magnesium stearate**, **mannitol**, methyl methacrylate, mint flavouring, polyethylene glycol, fumed silica, **silicon dioxide**, sodium starch glycolate, sodium stearyl fumarate, sorbitol or xylitol. The terms dispersing or dissolving as used herein to describe FDDFs. . .

SUMM . . . compound of the invention, a suitable powder base such as lactose or starch and a performance modifier such as 1-leucine, **mannitol** or **magnesium stearate**.

DETD . . . granulation of ingredients (a) to (c) and (a) to (d) with a solution of povidone, followed by addition of the **magnesium stearate** and compression.

Composition A

		mg/tablet	mg/tablet
(a)	Active ingredient	250	250
(b)	Lactose B.P.	210	26
(c)	Sodium Starch Glycollate	20	12
(d)	Povidone B.P.	15	9
(e)	**Magnesium Stearate**	5	3
		500	300

Composition B

		mg/tablet	mg/tablet
(a)	Active ingredient	250	250
(b)	Lactose 150	150	--
(c)	Avicel PH 101	60	26
(d)	Sodium Starch Glycollate	20	12
(e)	Povidone B.P.	15	9
(f)	**Magnesium Stearate**	5	3
		500	300

Composition C

	mg/tablet
Active ingredient	100
Lactose	200
Starch	50
Povidone	5
Magnesium Stearate	4
	359

DETD . . . admixed ingredients. The lactose used in formulation E is of the direct compression type.

Composition D

	mg/tablet
Active ingredient	250
Magnesium Stearate	4
Pregelatinised Starch NF15	146
	400

Composition E

	mg/tablet
Active ingredient	250
Magnesium Stearate	5
Lactose	145
Avicel	100
	500

Composition F (Controlled release composition)

		mg/tablet
(a)	Active ingredient	500
(b)	Hydroxypropylmethylcellulose (Methocel K4M Premium)	112
(c)	Lactose B.P.	53
(d)	Povidone B.P.C.	28
(e)	**Magnesium Stearate**	7
		700

DETD . . . be prepared by wet granulation of ingredients (a) to (c) with a solution of povidone, followed by addition of the **magnesium stearate** and compression.
DETD . . . may be prepared in a similar manner.

Composition B

		mg/capsule
(a)	Active ingredient	250
(b)	Lactose B.P.	143
(c)	Sodium Starch Glycollate	25
(d)	**Magnesium Stearate**	2
		420

Composition C

		mg/capsule
(a)	Active ingredient	250
(b)	Macrogol 4000 BP	350
		600

DETD . . . to cool to room temperature.

(vii) Pessary composition

	mg/pessary
Active ingredient (631 m)	250
Anhydrous Dextrose	380
Potato Starch	363
Magnesium Stearate	7

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DETD . . . expandable hydrophilic polymer, such as HPMC, methylcellulose (MC), carboxymethylcellulose sodium (CMC-Na), and poly(alkylene oxides), and/or an osmagent, such as NaCl, **mannitol**, dextrose, sodium tartrate, and sodium acetate. The layer surrounding and in contact with the core can comprise the active substance,. . .

DETD . . . lithium chloride, magnesium chloride, magnesium sulfate, lithium sulfate, potassium chloride, sodium sulfite, calcium bicarbonate, sodium sulfate, calcium sulfate, calcium lactate, d-**mannitol**, urea, tartaric acid, raffinose, sucrose, alpha-d-lactose monohydrate, glucose, combinations thereof and other similar or equivalent materials known to those of ordinary skill in the art. Preferred osmagents include potassium chloride, sodium tartrate, glucose, **mannitol**, sodium acetate, sodium chloride, sodium sulfate, sodium citrate, potassium tartrate, sorbitol, sucrose and combinations thereof.

DETD . . . used to impart sweetness to a preparation. Such compounds include, by way of example and without limitation, aspartame, dextrose, glycerin, **mannitol**, saccharin sodium, sorbitol, sucrose, fructose and other such materials known to those of ordinary skill in the art.

DETD . . . the punches and dies in a tableting machine during production. Such compounds include, by way of example and without limitation, **magnesium stearate**, calcium stearate, talc, glyceryl behenate, poly(ethylene glycol), hydrogenated vegetable oil, mineral oil, stearic acid, combinations thereof and other such materials. . .

DETD . . . preparation of tablets and capsules. Such compounds include, by way of example and without limitation, dibasic calcium phosphate, kaolin, sucrose, **mannitol**, microcrystalline cellulose, powdered cellulose, precipitated calcium carbonate, sorbitol, starch, combinations thereof and other such materials known to those of ordinary. . .

DETD . . . tablet formulations to reduce friction during tablet compression. Such compounds include, by way of example and without limitation, calcium stearate, **magnesium stearate**, mineral oil, stearic acid, zinc stearate, combinations thereof and other such materials known to those of ordinary skill in the. . .

DETD [0094] Representative anti-inflammatory and analgesic drugs include cortisone, hydrocortisone, prednisone, prednisolone, betamethasone, dexamethasone and fluorocortisone; cyclooxygenase II inhibitors such as **rofecoxib**, celecoxib, flosulide, NS-398, DUP-697, meloxicam, 6-methoxy-2-naphthylacetic acid, nabumetone, etodolac, nimesulide, SC-5766, SC-58215, T-614; salicylates such as salicylic acid, aspirin and. . .

DETD . . . of poly(ethylene oxide) (4,000,000 molecular weight), 2.15 g of poly(vinylpyrrolidone), 0.30 g of red ferric oxide, and 0.45 g of **silicon dioxide** were mixed then sieved through a 40-mesh screen. Alcohol (96.degree., 30 ml) was slowly added to the dry blend until. . . oven. The dried granulate was then sieved through a 20-mesh screen. The sieved granulate was mixed with 0.75 g of **magnesium stearate** and 0.45 g of **silicon dioxide** (both having been previously sieved through a 60-mesh screen) and then mixed in a V-blender for 5 minutes. The homogeneous. . .

DETD . . . of microcrystalline cellulose, 37.50 g. of sodium chloride, 45.00 g of poly(ethylene oxide) (200,000 molecular weight), 0.37 g of colloidal **silicon dioxide** and 15.75 g of poly(vinylpyrrolidone) were mixed and then sieved through a 40-mesh screen. The sieved mixture was then granulated. . . oven. Dried granulate was then sieved through a 20 mesh screen. The sieved mixture

was mixed with 1.25 g of **magnesium stearate** and 0.38 g of colloidal **silicon dioxide** (both previously sieved through a 60 mesh screen) in a V-blender for 5 minutes to form a homogeneous drug-containing composition.. . .

DETD . . . of poly(ethylene oxide) (300,000 molecular weight), 2.71 g of poly(vinylpyrrolidone), 0.35 g of red ferric oxide, and 0.53 g of **silicon dioxide** were mixed and sieved through a 40-mesh screen. Then, alcohol (96.degree.; 40 ml) was slowly added to the dry blend. . . C. in a conventional oven, and then sieved through a 20-mesh screen. The granulate was mixed with 0.88 g of **magnesium stearate** and 0.53 g of **silicon dioxide** (both after having been sieved through a 60 mesh screen) in a V-blender for 5 minutes. The homogeneous mixture was. . .

DETD . . . of microcrystalline cellulose, 32.05 g of sodium chloride, 37.50 g of poly(ethylene oxide) (200,000 molecular weight), 0.75 g of colloidal **silicon dioxide** and 19.25 g of poly(vinylpyrrolidone) were mixed and sieved through a 40 mesh screen. The sieved mixture was granulated with. . . and the dried granulate was sieved through a 20-mesh screen. The sieved blend was then mixed with 1.75 g of **magnesium stearate** and 0.75 g of colloidal **silicon dioxide** (both having been previously sieved through a 60-mesh screen) in a V-blender for 5 minutes. The homogeneous mixture was subsequently. . .

DETD . . . (4,000,000 molecular weight), 2.15 g of poly(vinylpyrrolidone), 0.30 g of red ferric oxide as coloring agent and 0.45 g of **silicon dioxide** were mixed, and the mix was sieved through a 40-mesh screen. Then, alcohol (96.degree.; 30 ml) was slowly added to. . . a convection oven for several hours. The dried granulate was sieved through a 20-mesh screen and mixed with 0.75 g **magnesium stearate** and 0.45 g **silicon dioxide** (both having been previously sieved through a 60-mesh screen) in a V-blender for 5 minutes. The homogeneous mixture was subsequently. . .

DETD . . . of microcrystalline cellulose, 37.5 g of sodium chloride, 45 g of poly(ethylene oxide) (200,000 molecular weight), 0.35 g of colloidal **silicon dioxide** and 12.00 g of poly(vinylpyrrolidone) were mixed. The blend was sieved through a 40-mesh screen. This mixture was granulated with. . . oven. Then the dry granulate was sieved through a 20-mesh screen. The sieved blend was mixed with 1.25 g of **magnesium stearate** and 0.40 g of colloidal **silicon dioxide** (having both been previously sieved through a 60 mesh screen) in a V-blender for 5 minutes. The homogeneous mixture was. . .

DETD . . . 4,000,000 molecular weight; 2.15 g of poly(vinylpyrrolidone); 0.30 g of red ferric oxide as coloring agent and 0.45 g of **silicon dioxide** were mixed and the mix was passed through a 40-mesh screen. Then, alcohol 96.degree. was slowly added to the dry. . . oven. Then the dry granulate was passed through a 20-mesh screen. The screened granulation was mixed with 0.75 g of **magnesium stearate** and 0.45 g of **silicon dioxide** (both previously passed through a 60-mesh screen) and placed into a V-blender for 5 minutes. The homogeneous mixture was subsequently. . .

DETD . . . cellulose; 37.50 g of sodium chloride; 45.00 g of polyethylene oxide having a 200,000 molecular weight; 0.37 g of colloidal **silicon dioxide** and 15.75 g of poly vinylpyrrolidone were mixed and the mix was passed through a 40-mesh screen. This mixture was. . .

DETD [0146] The screened blend was mixed with 1.25 g of **magnesium stearate** and 0.38 g of colloidal **silicon dioxide** (both previously passed through a 60-mesh screen) and placed into a V-blender for 5 minutes. The homogeneous mixture was

subsequently. . .

DETD . . . g of povidone, 8.00 g of polyethylene glycol 6000, 1.70 g of polyethylene glycol 400 and 1.00 g of colloidal **silicon dioxide**. The mixture was blended to homogenize; then, 2.00 g of **magnesium stearate** was added as lubricant. This blend was tabletted to 800 mg-1000 mg/core and hardness of 8-12 kP with flat faced,. . . passing through a standard USP 20-mesh screen and were blended with 122.30 g of microcrystalline cellulose, 0.50 g of colloidal **silicon dioxide**, 5.00 g of **croscarmellose** sodium and 2.00 g of **magnesium stearate**. This final blend was compressed over the film-coated tablets by compression using biconcaves, 13.0-mm diameter punches. Coating weight: 332 mg.. . .

DETD . . . 4,000,000 molecular weight; 2.15 g of poly(vinylpyrrolidone); 0.30 g of red ferric oxide as coloring agent and 0.45 g of **silicon dioxide** were mixed and the mix was passed through a 40-mesh screen. Then, alcohol 96.degree. was slowly added to the dry. . . oven. Then the dry granulate was passed through a 20-mesh screen. The screened granulation was mixed with 0.75 g of **magnesium stearate** and 0.45 g of **silicon dioxide** (both previously passed through a 60-mesh screen) and placed into a V-blender for 5 minutes. The homogeneous mixture was subsequently. . .

DETD . . . cellulose; 37.50 g of sodium chloride; 45.00 g of polyethylene oxide having a 200,000 molecular weight; 0.37 g of colloidal **silicon dioxide** and 15.75 g of poly(vinylpyrrolidone) were mixed and the mixture was passed through a 40-mesh screen. This mixture was granulated. . . oven. Then the dry granulate was passed through a 20-mesh screen. The screened blend was mixed with 1.25 g of **magnesium stearate** and 0.38 g of colloidal **silicon dioxide** (both previously passed through a 60-mesh screen) and placed into a V-blender for 5 minutes. The homogeneous mixture was subsequently. . .

DETD . . . g of povidone, 8.00 g of polyethylene glycol 6000, 1.70 g of polyethylene glycol 400 and 1.00 g of colloidal **silicon dioxide**. The mixture was blended to homogenize; then, 2.00 g of **magnesium stearate** was added as lubricant. This blend was tabletted to form 800 mg-1000 mg cores having a hardness of 8 -12. . . passing through a standard USP 20-mesh screen and were blended with 122.30 g of microcrystalline cellulose, 0.50 g of colloidal **silicon dioxide**, 5.00 g of **croscarmellose** sodium and 2.00 g of **magnesium stearate**. This final blend was compressed over the film-coated tablets by compression using biconcaves, 13.0-mm diameter punches. Coating weight: 332 mg.. . .

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SUMM . . . in U.S. Pat. No. 5,474,995 to Ducharme et al., including for example the compound 3-phenyl-4-[4-(methylsulfonyl)phenyl]-5H-furan-2-one, also referred to herein as **rofecoxib** (IV). ##STR3##

SUMM . . . challenges for formulation as fast-melt tablets. For example, many selective cyclooxygenase-2 inhibitory compounds, including celecoxib, deracoxib, valdecoxib, 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one, etoricoxib and **rofecoxib**, have very low solubility in aqueous media. In addition, some, for example celecoxib, have relatively high dose requirements. Celecoxib also. . .

SUMM . . . as required herein. Examples of saccharides of low moldability, at least when in finely particulate form without pre-granulation, include lactose, **mannitol**, glucose, sucrose, xylitol, etc.

SUMM . . . solubility dispersed in a matrix comprising a saccharide having low moldability, a saccharide having high moldability, and a glidant, preferably **silicon dioxide**. Such a composition can further comprise a wetting agent.

SUMM [0047] Illustratively, processes and compositions of the invention are suitable for celecoxib, deracoxib, valdecoxib, **rofecoxib**, etoricoxib, 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one, (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid and 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3-(2H)-pyridazinone, more particularly celecoxib, valdecoxib, **rofecoxib** and etoricoxib, and still more particularly celecoxib and valdecoxib.

SUMM . . . such drugs; for example in the case of valdecoxib in above-cited U.S. Pat. No. 5,633,272, and in the case of **rofecoxib** in above-cited U.S. Pat. No. 5,474,995.

SUMM [0094] Presently preferred low moldability saccharides include lactose and **mannitol**, particularly **mannitol** in its non-direct compression or powder form as described in Handbook of Pharmaceutical Excipients, 3rd Ed. (2000), Pharmaceutical Press, pp.. . .

SUMM . . . in the composition is therefore relatively low, a wetting agent may not be required, particularly if a glidant, for example **silicon dioxide**, is used.

SUMM [0106] **Magnesium stearate**, stearic acid and mixtures thereof are preferred water-insoluble lubricants.

SUMM . . . combination, starches, sodium starch glycolate, clays (such as Veegum.TM. HV), celluloses (such as purified cellulose, methylcellulose, sodium carboxymethylcellulose and carboxymethylcellulose), **croscarmellose** sodium, alginates, pregelatinized corn starches (such as NationalTM 1551 and National.TM. 1550), crospovidone, and gums (such as agar, guar, locust. . . step during the preparation of the composition, particularly prior to granulation or during a blending step prior to tablet compression. **Croscarmellose** sodium and sodium starch glycolate are preferred disintegrants.

SUMM [0116] Without being bound by theory, it is believed that, in some situations, glidants, for example talc or **silicon dioxide**, act to reduce interfacial tension between drug particles, having the effect of inhibiting and/or reducing drug agglomeration, act to decrease. . . rugosity of drug particles. See, for example, York (1975) J. Pharm. Sci., 64(7), 1216-1221. Use of a glidant such as **silicon dioxide**, therefore, can eliminate or reduce the need for a wetting agent in certain instances, for example, when formulating low dose. . .

SUMM [0117] **Silicon dioxide** is a preferred glidant. Suitable **silicon dioxide** products for use in preparing compositions of the invention include fumed silica or colloidal silica (e.g., Cab-O-Sil.TM. of Cabot Corp. and Aerosil.TM. of Degussa). **Silicon dioxide**, when present in compositions of the invention, is present in a total amount of about 0.05% to about 5%, preferably. . .

SUMM . . . or more pharmaceutically acceptable sweeteners. Non-limiting examples of sweeteners that can be used in compositions of the present invention include **mannitol**, propylene glycol, sodium saccharin, acesulfame K, neotame, aspartame, etc.

SUMM [0140] In this illustrative process, celecoxib and low moldability **mannitol** are de-lumped in a mill or grinder and blended to form a drug powder mixture. Next, this drug powder mixture. . .

SUMM [0143] Illustratively, in fluid bed granulation, celecoxib, low moldability **mannitol**, and any other desired excipients are mixed together and sized in a mill or grinder. Next, the resulting drug powder. . .

SUMM [0145] Alternatively, in high-shear wet granulation, celecoxib, **mannitol** and any other desired excipients are blended under high shear in a granulator. Next, a liquid solution of high moldability. . .

SUMM [0147] Whether fluid bed or high-shear granulation is used, the

celecoxib, low moldability **mannitol** and other excipients can, in an alternative process, be separately granulated and the resulting granules mixed together prior to compression.

DETD [0154] 1. Celecoxib and low moldability **mannitol** were de-lumped in a Co-mil producing a drug powder mixture.

DETD [0157] 4. The milled granulate was blended with flavoring agent (spearmint flavor), sweetening agent (acesulfame K) and lubricants (**magnesium stearate** and stearic acid) in a tumble blender for approximately 5 to 10 minutes to form a blend.

DETD . . . F2 F3 F4 F5 F6 F7

Tooling (mm)	11.1	11.1	12.7	12.7	11.1	11.1
Celecoxib	25.0	33.0	50.0	50.0	60.0	50.0
Mannitol.sup.1	66.75	58.75	40.25	41.75	31.75	41.75
Maltose	5.0	5.0	6.5	5.0	5.0	5.0
Magnesium stearate	0.75	0.75	0.75	0.75		0.75
Stearic acid	0.75	0.75	0.75	0.75	0.75	0.75
Sodium lauryl sulfate	1.0	1.0	1.0. . .	0.25	0.25	
Total (%)	100	100	100	100	100	100
Final Weight (mg)	400	400	400	400	400	400

.sub.1low moldability **mannitol**

DETD [0165] 1. Celecoxib, **silicon dioxide** and low moldability **mannitol** were de-lumped in a Co-mil producing a drug powder mixture.

DETD [0168] 4. The milled granulate was blended with flavoring agent (acesulfame K and peppermint flavor) and lubricants (**magnesium stearate** and stearic acid) in a tumble blender for about 5 minutes to form a blend.

DETD . . . 3

Composition (mg) of celecoxib fast-melt formulations F8 and F9

Formulation No.	F8	F9
Tooling (mm)	11.9	12
Celecoxib	200	200
Mannitol.sup.1	165	167
Maltose	20.0	20.0
Magnesium stearate	3.0	3.0
Silicon dioxide	2.0	2.0
Stearic acid	3.0	3.0
Sodium lauryl sulfate	4.0	2.0
Acesulfame K	2.0	2.0
Spearmint flavor	1.0	1.0
Total	400	400

.sup.1low moldability **mannitol**

DETD [0173] 1. Valdecoxib, **silicon dioxide** and low moldability **mannitol** were de-lumped in a Co-mil producing a drug powder mixture.

DETD [0176] 4. The milled granulate was blended with flavoring agent (acesulfame K and peppermint or spearmint flavor) and lubricants (**magnesium stearate** and stearic acid) in a tumble

blender for about 5 minutes to form a blend.

DETD . . .

TABLE 4

Composition (mg) of valdecoxib fast-melt formulations F10 and F11

Formulation No.	F10	F11
Tooling (mm)	11.9	11.9
Valdecoxib	40	40
Mannitol.sup.1	326	326
Maltose	20.0	20.0
Magnesium stearate	2.0	2.0
Silicon dioxide	2.0	2.0
Stearic acid	6.0	6.0
Acesulfame K	2.0	2.0
Spearmint flavor	2.0	--
Peppermint flavor	--	2.0
Total	400	400

.sup.1low moldability **mannitol**

CLM What is claimed is:

6. The process of claim 1 wherein the selective cyclooxygenase-2 inhibitory drug is selected from celecoxib, deracoxib, valdecoxib, **rofecoxib**, etoricoxib, 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one, (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid and 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3-(2H)-pyridazinone.

7. The process of claim 1 wherein the selective cyclooxygenase-2 inhibitory drug is selected from celecoxib, valdecoxib, **rofecoxib** and etoricoxib.

10. The process of claim 1 wherein said saccharide having low moldability is selected from lactose, **mannitol**, glucose, sucrose and xylitol.

11. The process of claim 1 wherein said saccharide having low moldability is **mannitol** of powder grade.

22. The process of claim 21 wherein said glidant is **silicon dioxide**.

50. The composition of claim 49 wherein said glidant is **silicon dioxide**.

56. The composition of claim 42 wherein the selective cyclooxygenase-2 inhibitory drug is selected from celecoxib, deracoxib, valdecoxib, **rofecoxib**, etoricoxib, 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one, (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid and 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3-(2H)-pyridazinone.

57. The composition of claim 42 wherein the selective cyclooxygenase-2 inhibitory drug is selected from celecoxib, valdecoxib, **rofecoxib** and etoricoxib.

64. The composition of claim 42 wherein said saccharide having low moldability is selected from lactose, **mannitol**, glucose,

sucrose and xylitol.

65. The composition of claim 42 wherein said saccharide having low moldability is **mannitol** of powder grade.

L1 ANSWER 7 OF 10 USPATFULL on STN

SUMM . . . developed. The most extensively characterized class of COX-2 selective inhibitor is diarylheterocycles, which include the recently approved drugs celecoxib and **rofecoxib**. However, other classes include, but are not limited to, acidic sulfonamides, indomethacin analogs, zomepirac analogs, chromene analogs and di-t-butylphenols. For. . .

DETD . . . No. 169590-42-5), valdecoxib (B-19; U.S. Pat. No. 5,633,272; CAS No. 181695-72-7), deracoxib (B-20; U.S. Pat. No. 5,521,207; CAS No. 169590-41-4), **rofecoxib** (B-21; CAS No. 162011-90-7), etoricoxib (MK-663; B-22; PCT publication WO 98/03484), JTE-522 (B-23), or a pharmaceutically acceptable salt or prodrug. . .

DETD [0121] In an even more preferred embodiment, the COX-2 selective inhibitor is selected from the group consisting of celecoxib, **rofecoxib** and etoricoxib.

DETD . . . ingredient. Examples of such dosage units are capsules, tablets, powders, granules or a suspension, with conventional additives such as lactose, **mannitol**, corn starch or potato starch; with binders such as crystalline cellulose, cellulose derivatives, acacia, corn starch or gelatins; with disintegrators such as corn starch, potato starch or sodium carboxymethyl-cellulose; and with lubricants such as talc or **magnesium stearate**. The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may. . .

DETD . . . form of a celecoxib formulation comprising one or more excipients such as diluents, e.g., lactose and/or microcrystalline cellulose, disintegrants, e.g., **croscarmellose** sodium, binding agents, e.g., polyvinylpyrrolidone, wetting agents, e.g., sodium lauryl sulfate, and lubricants, e.g., **magnesium stearate**.

DETD . . . or more excipients or alternatively the excipients can be added at a later step. For example, in tablet formulations where **croscarmellose** sodium is employed as a disintegrant, addition of a portion of the **croscarmellose** sodium during the blending step (providing intragranular **croscarmellose** sodium) and addition of the remaining portion after the drying step (providing extragranular **croscarmellose** sodium) can improve disintegration of the tablets produced. In this situation, preferably about 60% to about 75% of the **croscarmellose** sodium is added intragranularly and about 25% to about 40% of the **croscarmellose** sodium is added extragranularly. Similarly, for tablet formulations it has been discovered that addition of microcrystalline cellulose after the drying. . .

DETD . . . combination, lactose, including anhydrous lactose and lactose monohydrate; starches, including directly compressible starch and hydrolyzed starches (e.g., Celutab.TM. and Emdex.TM.); **mannitol**; sorbitol; xylitol; dextrose (e.g., Cerelose.TM. 2000) and dextrose monohydrate; dibasic calcium phosphate dihydrate; sucrose-based diluents; confectioner's sugar; monobasic calcium sulfate. . .

DETD [0571] A composition of the invention optionally comprises one or more pharmaceutically acceptable sweeteners. Non-limiting examples of suitable sweeteners include **mannitol**, propylene glycol, sodium saccharin, acesulfame K, neotame and aspartame. Alternatively or in addition, a viscous sweetener such as sorbitol solution,. . .

DETD . . . 1550, and Colocorn.TM. 1500), clays (e.g., Veegum.TM. HV), celluloses such as purified cellulose, microcrystalline cellulose, methylcellulose, carboxymethylcellulose and sodium

carboxymethylcellulose, **croscarmellose** sodium (e.g., Ac-Di-Sol.TM. of FMC), alginates, crospovidone, and gums such as agar, guar, locust bean, karaya, pectin and tragacanth gums.

DETD [0576] **Croscarmellose** sodium is a preferred disintegrant for tablet or capsule disintegration, and, if present, preferably constitutes about 0.2% to about 10%,. . . . 0.2% to about 7%, and still more preferably about 0.2% to about 5%, of the total weight of the composition. **Croscarmellose** sodium confers superior intragranular disintegration capabilities to granulated compositions of the present invention.

DETD [0584] Glidants can be used to promote powder flow of a solid formulation. Suitable glidants include colloidal **silicon dioxide**, starch, talc, tribasic calcium phosphate, powdered cellulose and magnesium trisilicate. Colloidal **silicon dioxide** is particularly preferred.

DETD [0585] **Magnesium stearate** is a preferred lubricant used, for example, to reduce friction between the equipment and granulated mixture during compression of tablet. . .

DETD . . . #310

microcrystalline cellulose NF (Avicel .TM. PH-101)	secondary diluent	60
pregelatinized starch NF (National Starch 1500)	binding agent	20
croscarmellose sodium NF (Ac-Di-Sol .TM.)	disintegrant	4
magnesium stearate	lubricant	1
Total tablet weight		200

DETD . . . 14 screen using a Quadro comil at medium speed, and then placed in a Patterson Kelley V-blender together with the **croscarmellose** sodium. The V-blender was operated for about 5 minutes to thoroughly mix the **croscarmellose** sodium with the granules; then **magnesium stearate** was added with further mixing for about 3 minutes to prepare a lubricated blend. This was compressed on a Manesty. . .

DETD . . . 60

cellulose NF (Avicel .TM. PH-101)	diluent	
intragranular		30
extragranular		30
pregelatinized starch NF (National Starch 1500)	binding agent	20
croscarmellose sodium NF (Ac-Di-Sol .TM.)	disintegrant	6
intragranular		3
extragranular		3
magnesium stearate	lubricant	1
Total tablet weight		200

DETD [0676] The micronized valdecoxib, lactose monohydrate, intragranular microcrystalline cellulose, pregelatinized starch and intragranular **croscarmellose** sodium were mixed in a Baker Perkins high shear mixer at high impeller/chopper speed for about 3 minutes to form. . . was then placed in a Patterson Kelley V-blender. Here, the granulate was mixed with the extragranular microcrystalline cellulose and extragranular **croscarmellose** sodium for about 5 minutes, and then with the **magnesium stearate** for a further 3 minutes, to form a lubricated blend. This was compressed on a Korsch PH-230 rotary press using. . .

DETD . . . 40

Lactose monohydrate NF	108	103	206	186

Microcrystalline cellulose NF	60	60	120	120
Pregelatinized starch NF	20	20	40	40
Croscarmellose sodium NF	6	6	12	12
Magnesium stearate NF	1	1	2	2
Total weight (excluding coating)	200	200	400	400
Opadry Yellow YS-1-12525A	6			12
Opadry White YS-1-18027A		6. . .		

CLM What is claimed is:

. . . The combination of claim 6 wherein the selective cyclooxygenase-2 inhibitor is a compound selected from the group consisting of celecoxib, **rofecoxib**, valdecoxib, deracoxib, etoricoxib, 2-(3,4-Difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone, parecoxib, and meloxicam.

. . . 39. The combination of claim 38 wherein the compound is selected from the group consisting of celecoxib, deracoxib, valdecoxib and **rofecoxib**.

. . . The method of claim 106 wherein the selective cyclooxygenase-2 inhibitor is a compound selected from the group consisting of celecoxib, **rofecoxib**, valdecoxib, deracoxib, etoricoxib, 2-(3,4-Difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone, parecoxib, and meloxicam.

L1 ANSWER 8 OF 10 USPATFULL on STN

SUMM . . . in U.S. Pat. No. 5,474,995 to Ducharme et al., including for example the compound 3-phenyl-4-[4-(methylsulfonyl)phenyl]-5H-furan-2-one, also referred to herein as **rofecoxib** (IV). (IV) ##STR3##

SUMM . . . challenges for formulation as fast-melt tablets. For example, many selective cyclooxygenase-2 inhibitory compounds, including celecoxib, deracoxib, valdecoxib, 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one, etoricoxib and **rofecoxib**, have very low solubility in aqueous media. In addition, some, for example celecoxib, have relatively high dose requirements. Celecoxib also. . .

DETD [0077] Illustratively, processes and compositions of the invention are suitable for celecoxib, deracoxib, valdecoxib, **rofecoxib**, etoricoxib, 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one, (S)-6,8-dichloro-2-(trifluoromethyl) -2H-1-benzopyran-3-carboxylic acid and 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5- [4-(methylsulfonyl)phenyl]-3-(2H)-pyridazinone, more particularly celecoxib, valdecoxib, **rofecoxib** and etoricoxib, and still more particularly celecoxib and valdecoxib.

DETD . . . such drugs; for example in the case of valdecoxib in above-cited U.S. Pat. No. 5,633,272, and in the case of **rofecoxib** in above-cited U.S. Pat. No. 5,474,995.

DETD . . . mono-, di-and oligosaccharides having up to 6 saccharide units, including sugars and sugar alcohols, e.g., erythritol, glucose, lactose, maltitol, maltose, **mannitol**, sorbitol, sucrose, xylitol, etc.

DETD . . . sugars and sugar alcohols having low moldability, particularly when in finely particulate as opposed to granular form, e.g., glucose, lactose, **mannitol**, sucrose and xylitol, can be useful.

DETD [0127] **Magnesium stearate**, stearic acid and mixtures thereof are preferred water-insoluble lubricants.

DETD . . . the invention include starches, sodium starch glycolate, clays, e.g., Veegum.TM. Hv, celluloses, e.g., purified cellulose, methylcellulose, sodium carboxymethylcellulose carboxymethylcellulose, etc., **croscarmellose** sodium, alginates, pregelatinized corn

starches, e.g., National.TM. 1551 and National.TM. 1550, crospovidone, gums, e.g., agar, guar, locust bean, karaya, pectin and tragacanth gums, and mixtures thereof. **Croscarmellose** sodium and sodium starch glycolate are preferred disintegrants.

DETD . . . tablet dies, to prevent sticking of tableting material to punches and dies, or to produce tablets having a sheen, include **silicon dioxide** products such as fumed silica (e.g., Cab-O-Sil.TM. of Cabot Corp. and Aerosil.TM. of Degussa). **Silicon dioxide**, if desired, is present in a molded article of the invention in a total amount of about 0.05% to about. . .

DETD . . . acceptable sweeteners that can optionally be present in a molded article of the invention in a sweetening effective amount include **mannitol**, propylene glycol, sodium saccharin, acesulfame K, neotame, aspartame, etc.

DETD . . . comprises a mass of spun fibers of a readily water-soluble material, for example a sugar such as sucrose, fructose, dextrose, **mannitol**, sorbitol, lactose, maltose, etc. or a cellulosic material such as methylcellulose, ethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, alkali metal salts of carboxymethylcellulose, etc.,. . .

DETD . . . process, from a feedstock comprising a saccharide component, for example sucrose optionally mixed with other saccharides such as dextrose, sorbitol, **mannitol**, etc., optionally with a crystallization enhancer such as a surfactant; adding a crystallization/binding promoter such as an alcohol, e.g., ethanol,. . .

DETD . . . the molded article comprises an open matrix network having the drug distributed therein, the open matrix network being formed from **mannitol** in admixture with a gum, for example acacia, guar gum, xanthan gum, tragacanth gum, locust bean gum, pectin, algin, agar,. . .

DETD . . . matrix that comprises a gum, for example acacia, guar gum, xanthan gum, tragacanth gum, etc., a carbohydrate base, for example **mannitol**, dextrose, sucrose, lactose, maltose, maltodextrin, corn syrup solids, etc., and a solvent; shaping the mixture to form a tablet; freezing. . .

DETD . . . the invention, the molded article is prepared by a process comprising suspending the drug and a sugar comprising lactose and/or **mannitol** in a 0.3% to 2% by weight aqueous solution of agar used in an amount of 40% to 60% by. . .

DETD . . . comprising the drug and a compound which is sweet in taste and has a negative heat of solution, for example **mannitol**, and a coating comprising a film-forming polymer such as ethylcellulose, substantially as disclosed in above-cited U.S. Pat. No. 5,607,697. This. . .

DETD . . . readily water-soluble crystalline or powdery solid, preferably one having a sweet taste such as sucrose, lactose, glucose, fructose, xylitol, sorbitol, **mannitol**, etc., with a suitable amount of water, typically about 1% to about 10% by weight of the tablet components; compressively. . .

DETD . . . to second polymer of about 90:10 to about 50:50; dry-blending the coated drug particles with a compressible carbohydrate, for example **mannitol**, sorbitol, dextrose, sucrose, xylitol, lactose, etc., and a binder, for example cellulose (in particular microcrystalline cellulose), cellulosic derivatives, polyvinylpyrrolidone, starch,. . .

DETD . . . spray-drying a feedstock comprising a carbohydrate, for example a saccharide of low or high moldability such as maltose, maltitol, sorbitol, **mannitol**, glucose, sucrose, xylitol, etc., and optionally a low density alkaline-earth metal salt; and a step of compressing the compact granules,. . .

DETD . . . compression and comprising the drug, a non-direct compression

filler, preferably a non-direct compression sugar or sugar alcohol such as dextrose, **mannitol**, sorbitol, lactose, sucrose, etc., and a lubricant, substantially as disclosed in above-cited U.S. Pat. No. 6,024,981.

CLM What is claimed is:

4. The molded article of claim 1 wherein the selective cyclooxygenase-2 inhibitory drug is selected from celecoxib, deracoxib, valdecoxib, **rofecoxib**, etoricoxib, 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one, (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid and 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methyl- 1 -butoxy)-5-[4-(methylsulfonyl)phenyl]-3-(2H)-pyridazinone.

5. The molded article of claim 1 wherein the selective cyclooxygenase-2 inhibitory drug is selected from celecoxib, valdecoxib, **rofecoxib** and etoricoxib.

. . . The molded article of claim 13 wherein the sugar or sugar alcohol is selected from erythritol, glucose, lactose, maltitol, maltose, **mannitol**, sorbitol, sucrose and xylitol.

27. The process of claim 24 wherein the selective cyclooxygenase-2 inhibitory drug is selected from celecoxib, deracoxib, valdecoxib, **rofecoxib**, etoricoxib, 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one, (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid and 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methyl- 1 -butoxy)-5-[4-(methylsulfonyl)phenyl]-3-(2H)-pyridazinone.

28. The process of claim 24 wherein the selective cyclooxygenase-2 inhibitory drug is selected from celecoxib, valdecoxib, **rofecoxib** and etoricoxib.

. . . 37. The process of claim 36 wherein the sugar or sugar alcohol is selected from erythritol, glucose, lactose, maltitol, maltose, **mannitol**, sorbitol, sucrose and xylitol.

L1 ANSWER 9 OF 10 USPATFULL on STN

SUMM . . . in U.S. Pat. No. 5,474,995 to Ducharme et al., including for example the compound 3-phenyl-4-[4-(methylsulfonyl)phenyl]-5H-furan-2-one, also referred to herein as **rofecoxib** (IV). ##STR3##

SUMM . . . challenges for formulation as fast-melt tablets. For example, many selective cyclooxygenase-2 inhibitory compounds, including celecoxib, deracoxib, valdecoxib, 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one, etoricoxib and **rofecoxib**, have very low solubility in aqueous media. In addition, some, for example celecoxib, have relatively high dose requirements. Celecoxib also. . .

SUMM . . . as required herein. Examples of saccharides of low moldability, at least when in finely particulate form without pre-granulation, include lactose, **mannitol**, glucose, sucrose, xylitol, etc.

DETD [0037] Illustratively, processes and compositions of the invention are suitable for celecoxib, deracoxib, valdecoxib, **rofecoxib**, etoricoxib, 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one, (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid and 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3-(2H)-pyridazinone, more particularly celecoxib, valdecoxib, **rofecoxib** and etoricoxib, and still more particularly celecoxib and valdecoxib.

DETD . . . such drugs; for example in the case of valdecoxib in above-cited U.S. Pat. No. 5,633,272, and in the case of

rofecoxib in above-cited U.S. Pat. No. 5,474,995.

DETD [0075] Presently preferred low moldability saccharides include lactose and **mannitol**, particularly **mannitol** in its non-direct compression or powder form as described in Handbook of Pharmaceutical Excipients, 3rd Ed. (2000), Pharmaceutical Press, pp.. . .

DETD . . . can be used in mixture with a wetting agent, as for example in calcium stearate/sodium lauryl sulfate mixtures (e.g., Sterowet.TM.). **Magnesium stearate**, stearic acid and mixtures thereof are preferred lubricants.

DETD . . . combination, starches, sodium starch glycolate, clays (such as Veegum.TM. HV), celluloses (such as purified cellulose, methylcellulose, sodium carboxymethylcellulose and carboxymethylcellulose), **croscarmellose** sodium, alginates, pregelatinized corn starches (such as National.TM. 1551 and National.TM. 1550), crospovidone, and gums (such as agar, guar, locust. . . step during the preparation of the composition, particularly prior to granulation or during a blending step prior to tablet compression. **Croscarmellose** sodium and sodium starch glycolate are preferred disintegrants.

DETD [0087] Compositions of the present invention optionally comprise one or more pharmaceutically acceptable glidants, for example talc or **silicon dioxide**, to enhance flow of tableting material into tablet dies, to prevent sticking of tableting material to punches and dies, or. . .

DETD . . . or more pharmaceutically acceptable sweeteners. Non-limiting examples of sweeteners that can be used in compositions of the present invention include **mannitol**, propylene glycol, sodium saccharin, acesulfame K, neotame, aspartame, etc.

DETD [0102] In this illustrative process, celecoxib and low moldability **mannitol** are de-lumped in a mill or grinder and blended to form a drug powder mixture. Next, this drug powder mixture. . .

DETD [0104] Illustratively, in fluid bed granulation, celecoxib, low moldability **mannitol**, and any other desired excipients are mixed together and sized in a mill or grinder. Next, the resulting drug powder. . .

DETD [0106] Alternatively, in high-shear wet granulation, celecoxib, **mannitol** and any other desired excipients are blended under high shear in a granulator. Next, a liquid solution of a binding. . .

CLM What is claimed is:

5. The process of claim 1 wherein the selective cyclooxygenase-2 inhibitory drug is selected from celecoxib, deracoxib, valdecoxib, **rofecoxib**, etoricoxib, 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one, (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid and 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3-(2H)-pyridazinone.

6. The process of claim 1 wherein the selective cyclooxygenase-2 inhibitory drug is selected from celecoxib, valdecoxib, **rofecoxib** and etoricoxib.

13. The process of claim 1 wherein said saccharide having low moldability is selected from lactose, **mannitol**, glucose, sucrose and xylitol.

14. The process of claim 1 wherein said saccharide having low moldability is **mannitol** of powder grade.

22. The composition of claim 19 wherein the selective cyclooxygenase-2 inhibitory drug is selected from celecoxib, deracoxib, valdecoxib, **rofecoxib**, etoricoxib, 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one, (S)-6,8-dichloro-2-

(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid and 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl] -3-(2H)-pyridazinone.

23. The composition of claim 19 wherein the selective cyclooxygenase-2 inhibitory drug is selected from celecoxib, valdecoxib, **rofecoxib** and etoricoxib.

30. The composition of claim 19 wherein said saccharide having low moldability is selected from lactose, **mannitol**, glucose, sucrose and xylitol.

31. The composition of claim 19 wherein said saccharide having low moldability is **mannitol** of powder grade.

L1 ANSWER 10 OF 10 USPATFULL on STN

DETD . . . combination, lactose, including anhydrous lactose and lactose monohydrate; starches, including directly compressible starch and hydrolyzed starches (e.g., Celutab.TM. and Emdex.TM.); **mannitol** ; sorbitol; xylitol; dextrose (e.g., Cerelose.TM. 2000) and dextrose monohydrate; dibasic calcium phosphate dihydrate; sucrose-based diluents; confectioner's sugar; monobasic calcium sulfate. . .

DETD . . . 1550, and Colocorn.TM. 1500), clays (e.g., Veegum.TM. HV), celluloses such as purified cellulose, microcrystalline cellulose, methylcellulose, carboxymethylcellulose and sodium carboxymethylcellulose, **croscarmellose** sodium (e.g., Ac-Di-Sol.TM. of FMC), alginates, crospovidone, and gums such as agar, guar, locust bean, karaya, pectin and tragacanth gums.

DETD [0066] **Croscarmellose** sodium is a preferred disintegrant for tablet or capsule disintegration, and, if present, preferably constitutes about 0.2% to about 10%,. . . 0.2% to about 7%, and still more preferably about 0.2% to about 5%, of the total weight of the composition. **Croscarmellose** sodium confers superior intragranular disintegration capabilities to granulated compositions of the present invention.

DETD [0072] **Magnesium stearate** is a preferred lubricant used, for example, to reduce friction between the equipment and granulated mixture during compression of tablet. . .

DETD [0074] Glidants can be used to promote powder flow of a solid formulation. Suitable glidants include colloidal **silicon dioxide**, starch, talc, tribasic calcium phosphate, powdered cellulose and magnesium trisilicate. Colloidal **silicon dioxide** is particularly preferred.

DETD . . . composition of the invention can also be administered in combination with a second selective COX-2 inhibitory drug, for example valdecoxib, **rofecoxib**, etc.